C–N Bond formation

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A General Catalytic Hydroamidation of 1,3-Dienes: Atom-Efficient Synthesis of *N*-Allyl Heterocycles, Amides, and Sulfonamides**

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Abstract: *Transition-metal-catalyzed hydroamination reactions are sustainable and atom-economical C–N bond-forming processes. Although remarkable progress has been made in the inter- and intramolecular amination of olefins and 1,3-dienes, related intermolecular reactions of amides are still much less known. Control of the regioselectivity without analogous telomerization is the particular challenge in the catalytic hydroamidation of alkenes and 1,3-dienes. Herein, we report a general protocol for the hydroamidation of electron-deficient N-heterocyclic amides and sulfonamides with 1,3-dienes and vinyl pyridines in the presence of a catalyst derived from [{Pd(π-cinnamyl)Cl}$_2$] and ligand* ***L7*** *or* ***L10****. The reactions proceeded in good to excellent yield with high regioselectivity. The practical utility of our method is demonstrated by the hydroamidation of functionalized biologically active substrates. The high regioselectivity for linear amide products makes the procedure useful for the synthesis of a variety of allylic amides.*

The selective construction of C–N bonds continues to be an important goal in catalysis and organic synthesis. Most well-established methodologies for the synthesis of amides and related compounds rely on the condensation of acids with amines in the presence of activating/dehydration reagents and involve significant amounts of waste generation. In contrast, the direct addition of N–H bonds to unsaturated C–C bonds, commonly known as hydroamination, is a more sustainable and atom-efficient process.[1] Especially in the last two decades, the utility of catalytic hydroamination reactions has been extensively explored. On the basis of elegant mechanistic investigations, several intramolecular reactions have been developed.[2] Despite notable progress in this area,[3,4] the development of a general intermolecular process with non-activated alkenes is still a challenging task.[5] On the other hand, simple base-catalyzed hydroamination reactions with 1,3-dienes or styrenes proceed smoothly owing to the increased stabilization of the anionic intermediate. In fact, the best-known example of an intermolecular hydroamination is the synthesis of an intermediate for the Takasago (–)-menthol process.[6] As compared to analogous reactions of amines,[7] the selective addition of electron-deficient N-heterocycles, amides, and sulfonamides to olefins and dienes is scarce and has rarely been investigated.[8] To the best of our knowledge, no hydroamidation reactions of 1,3-dienes in the presence of palladium catalysts exist.

On the basis of our long-standing interest in the catalytic hydroamination of alkynes,[9] and our recent studies on the synthesis of allylic amines by the palladium-catalyzed amination of allylic alcohols,[10] we became interested in the related hydroamidation of 1,3-dienes (Scheme 1). Unfortunately, the use of previous catalyst systems for the hydroamidation of isoprene was not successful. However, [{Pd(π-cinnamyl)Cl}$_2$] in the presence of 1,3-bis(diphenylphosphino)propane (**L7**) or 1,4-bis(dicyclohexylphosphino)butane (**L10**) enabled the general and regioselective 1,4-addition of a variety of electron-deficient N-heterocycles, cyclic and acyclic amides, and sulfonamides.

At the start of this study, we investigated the intermolecular hydroamidation of isoprene (**1a**) and 4-methylphthalimide (**2a**) as a model reaction in the presence of [{Pd(π-cinnamyl)Cl}$_2$] and different phosphine ligands **L1**–**L15** (Scheme 2). The application of monodentate ligands **L1**–**L3** resulted in no conversion. Similarly, ligands **L4** and **L5** containing a biaryl backbone gave no desired product **3a**. Also, various bidentate ligands, for example, 1,4-bis(diphenylphosphino)butane (dppb, **L8**), 1,5-bis(diphenylphosphino)pentane (dpppent, **L9**), and **L15** proved to be catalytically inert. However, 1,4-bis(dicyclohexylphosphino)butane (**L10**), 1,2-bis(diphenylphosphinomethyl)benzene (**L11**), **L12**, Xantphos (**L13**), DPEphos (**L14**), and 1,2-bis(diphenylphosphino)-ethane (**L6**) gave the desired product **3a** in 5–60% yield. Notably, the best results were obtained using 1,3-bis(diphenylphosphino)propane (**L7**) and gave 75% yield of **3a** as a single regioisomer.

Next, we studied the influence of different catalyst precursors, solvents, and temperatures for the intermolecular hydroamidation with **L7** as the most promising ligand (selected results are summarized in Table 1). The use of a number of different Pd^{II} and Pd^0 precursors led to poor or no product yield. [{Pd(π-cinnamyl)Cl}$_2$] was identified as the best precatalyst (Table 1, entries 1–6). The choice of solvent also played a crucial role in the hydroamidation reaction; for example, applying 1,4-dioxane did not result in any product of **3a** (Table 1, entry 7). However, the use of *tert*-amyl alcohol and *n*-heptane gave **3a** in 34 and 75% yield, respectively (Table 1, entries 8 and 9). The optimal result was achieved in toluene. We studied the influence of different bases and found that inexpensive Na_2CO_3 afforded **3a** in 80% yield (Table 1,

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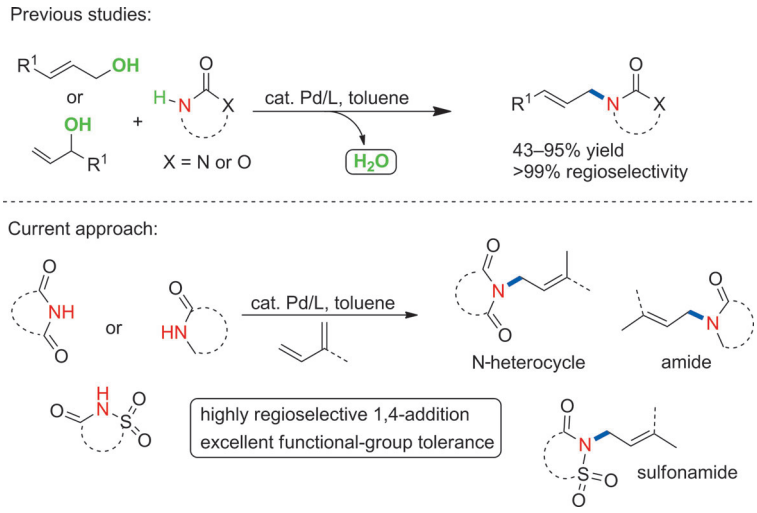
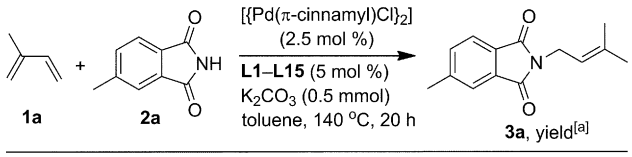
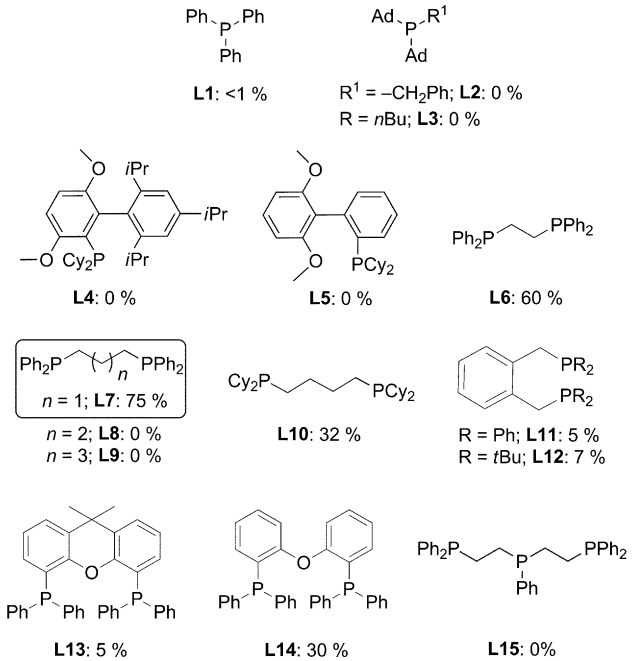


Scheme 1. Palladium-catalyzed regioselective synthesis of allylic amides.





Scheme 2. Palladium-catalyzed intermolecular hydroamidation of **1a** with 4-methylphthalimide (**2a**): Influence of the ligand. [a] Yield of the isolated product. Ad = adamantyl, Cy = cyclohexyl.

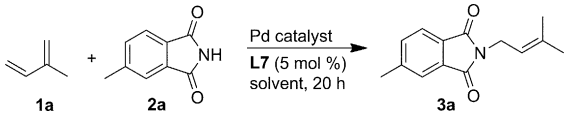
entries 1 and 10–13). It was possible to run the benchmark reaction with a lower catalyst loading, but we found that the use of 2.5 mol% of the Pd catalyst was optimal, with the formation of the 1,4-addition product **3a** as a single regioisomer in 80% yield (Table 1, entry 10). Prolongation of the reaction time led to the formation of other regioisomers of similar molecular mass, as observed by GC–MS analysis of the crude reaction mixture. As expected, we did not observe any product in the absence of a catalyst or ligand. The absence of a base also resulted in a poor product yield (Table 1, entries 16–18).

To exclude the possibility that this reaction was promoted by simple base catalysis, we also studied the model reaction in the presence of *n*BuLi (5 mol%), but did not observe any desired product.[1f,11] Furthermore, the reaction of [{Pd(π-allyl)Cl}$_2$] in combination with **L13**, as described by Hartwig and co-workers,[7f] did not give any product **3a**, too (Table 1, entry 20). Notably, the reaction with the defined complex [(dppp)Pd(π-cinnamyl)Cl] gave the 1,4-addition product **3a** in 70% yield as a single regioisomer (Table 1, entry 21).

In all reactions in which we observed lower yields of **3a**, nonreacted 4-methylphthalimide was recovered. Notably, in some screening experiments, we also observed the formation of 5–10% of the branched regioisomer along with 2–5% of the homoallylic amide.

These promising results for the model reaction prompted us to study the intermolecular hydroamidation of isoprene **1a**

Table 1: Palladium-catalyzed intermolecular hydroamidation of **1a** with 4-methylphthalimide (**2a**): Investigation of reaction conditions.[a]



Entry	Catalyst (mol%)	Solvent	Base	Yield [%][b]
1	[{Pd(π-cinnamyl)Cl}$_2$] (2.5)	toluene	K_2CO_3	75
2	$Pd(OAc)_2$ (2.5)	toluene	K_2CO_3	0
3	[$PdCl_2(PPh_3)_2$] (2.5)	toluene	K_2CO_3	0
4	[Pd(cod)Cl$_2$] (2.5)	toluene	K_2CO_3	0
5	[$Pd(dba)_2$] (2.5)	toluene	K_2CO_3	11
6	[{Pd(π-allyl)Cl}$_2$] (2.5)	toluene	K_2CO_3	55
7	[{Pd(π-cinnamyl)Cl}$_2$] (2.5)	1,4-dioxane	K_2CO_3	0
8	[{Pd(π-cinnamyl)Cl}$_2$] (2.5)	*tert*-amyl alcohol	K_2CO_3	34
9	[{Pd(π-cinnamyl)Cl}$_2$] (2.5)	*n*-heptane	K_2CO_3	75
10	[{Pd(π-cinnamyl)Cl}$_2$] (2.5)	toluene	Na_2CO_3	80
11	[{Pd(π-cinnamyl)Cl}$_2$] (2.5)	toluene	NaOAc	0
12	[{Pd(π-cinnamyl)Cl}$_2$] (2.5)	toluene	K_3PO_4	61
13	[{Pd(π-cinnamyl)Cl}$_2$] (2.5)	toluene	Et_3N	41
14	[{Pd(π-cinnamyl)Cl}$_2$] (2)	toluene	Na_2CO_3	65
15	[{Pd(π-cinnamyl)Cl}$_2$] (1)	toluene	Na_2CO_3	50
16	no catalyst	toluene	Na_2CO_3	0
17[c]	[{Pd(π-cinnamyl)Cl}$_2$] (2.5)	toluene	Na_2CO_3	0
18	[{Pd(π-cinnamyl)Cl}$_2$] (2.5)	toluene	–	7
19[d]	[{Pd(π-cinnamyl)Cl}$_2$] (2.5)	toluene	Na_2CO_3	0
20[e]	[{Pd(π-allyl)Cl}$_2$] (1)	THF	–	0
21[f]	[(dppp)Pd(π-cinnamyl)Cl]	toluene	Na_2CO_3	70

[a] Reaction conditions: **1a** (4 mmol), **2a** (1 mmol), Pd catalyst (1–2.5 mol%), base (50 mol%), 120°C, solvent (3.0 mL). [b] Yield of the isolated product. [c] No ligand was used. [d] The reaction was carried out at 100°C. [e] The reaction was carried out with **L13** (2 mol%) at 23°C for 20 h. [f] The reaction was carried out with 5 mol% of the palladium complex. cod = 1,5-cyclooctadiene, dba = dibenzylideneacetone.

with anilines and a range of electron-poor N-heterocycles, including imides, ureas, amides, and sulfonamides (selected results are summarized in Table 2). While the reactions of aniline, *p*-anisidine, and *p*-trifluoromethylaniline did not provide the desired products, the reaction of phthalimide (**2b**) with isoprene resulted in the selective formation of **3b** in 76% yield (Table 2, entry 1). Similarly, tetramethylenegluterimide (**2c**) and succinimide (**2d**) reacted well in this process to afford the respective products **3c**–**3d** in 60–90% yield (Table 2, entries 2 and 3). Under similar reaction conditions, the bicyclic amide **2e** was converted into **3e** in 55% yield (Table 2, entry 4).

Next, we tried to extend the scope of the methodology to the use of simple amides. Unfortunately, the reaction of **1a** with *N*-phenylacetamide (**2f**) did not result in any of product **3f** under similar reaction conditions. However, when the reaction was carried out with the ligand **L10** in *n*-heptane, **3f** was obtained as a single isomer in 70% yield (Table 2, entry 5; see the Supporting Information for details). Further reactions with aromatic amides were also successful and gave **3g**–**3h** in 65 and 45% yield, respectively (Table 2, entries 6 and 7).

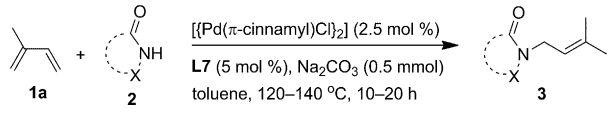
To demonstrate the generality of this optimized protocol, we tested a series of functionalized sulfonamide derivatives as nucleophiles. The sulfonamide group is found as an essential structural motif in medicinal chemistry and plays a key role in pharmacological studies.[12] Thus, the use and functionalization of sulfonamide-based molecules is an important tactical tool in medicinal chemistry. Gratifyingly, the reaction of **1a** with 4-Cl-, 2-Br-, or 2-CN-substituted phenyl sulfonamides **2i**–**2k** as well as saccharin (**2l**) gave **3i**–**3l** in 75–90% yield (Table 2, entries 8–11). In some of these reactions, we also observed a minor amount (2–5%) of the branched regioisomer. In cases where we observed lower product yield, corresponding starting materials were recovered from the reaction mixture.

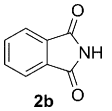
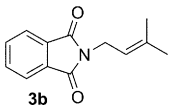
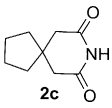
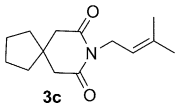
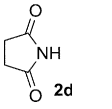
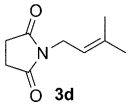
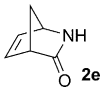
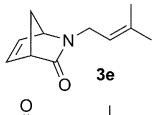
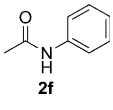
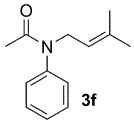
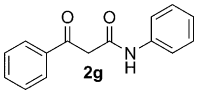
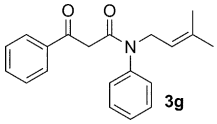
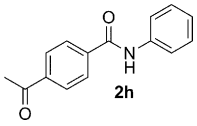
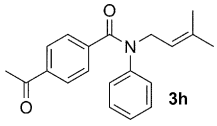
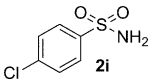
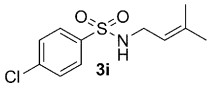
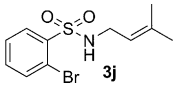
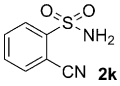
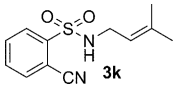
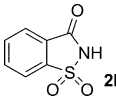
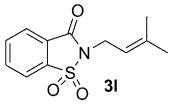
Further to explore the scope of our optimized catalytic system, we used a series of different 1,3-dienes as well as 2- and 4-vinylpyridine. The reaction of methyl- or phenyl-substituted butadiene **1b**–**1c** with phthalimide derivatives resulted in the formation of **3m**–**3n** in 45–52% yield, respectively (Table 3, entries 1 and 2). Whereas the reaction of **2b** with 3-methyl-1,3-pentadiene (**1d**) gave **3o** in 50% yield (Table 3, entry 3), 2,3-dimethyl butadiene (**1e**) reacted with phthalimide to give **3p** in 90% yield (Table 3, entry 4). To our delight, the use of inexpensive 7-methyl-3-methylene-1,6-octadiene (myrcene, **1f**) with **2b** led selectively to the linear geranylamine derivative **3q** in 66% yield (Table 3, entry 5).[6] The methyl-ester-substituted diene derivatives methyl 2,4-pentadienoate (**1g**) and methyl sorbate (**1h**) resulted in 70 and 65% yield of **3r**–**3s** (Table 3, entries 6 and 7). Under similar reaction conditions, the reaction of 1,3-cyclohexadiene (**1i**) with **2a** and **2b** gave **3t**–**3u** in 80–90% yield (Table 3, entries 8 and 9).

Next, we tested related vinyl arenes as substrates. Gratifyingly, 2-vinyl- and 4-vinylpyridine (**1j**–**1k**) reacted well and afforded the corresponding linear amides **3v**–**3w** in 50–87% yield (Table 3, entries 10 and 11).[13] We believe this transformation constitutes the first example of the intermolecular hydroamidation of vinyl pyridines with electron-poor phthalimides.

Having studied the intermolecular 1,4-hydroamidation of 1,3-dienes and the anti-Markovnikov hydroamidation of vinyl pyridines, we were interested in gaining insight into the reaction mechanism. Initially, we prepared the defined [(dppp)Pd(π-cinnamyl)Cl] complex and studied the hydroamination reaction with 4-methylphthalimide (**2a**). The

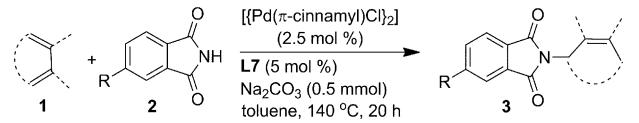
Table 2: Intermolecular hydroamidation of **1a** with N-heterocycles, amides, and sulfonamides.[a]

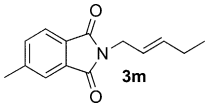
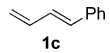
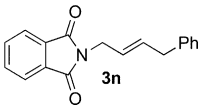
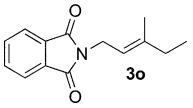
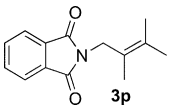
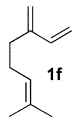
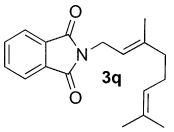
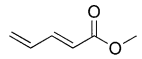
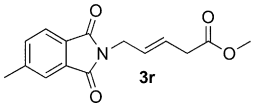
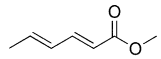
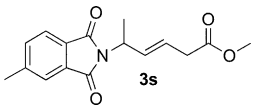
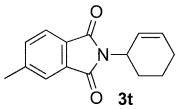
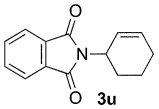
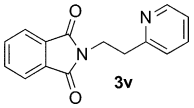
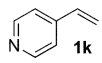
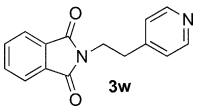


Entry	Nucleophile **2**	Product **3**	Yield [%][b]
1[c]	 **2b**	 **3b**	76
2	 **2c**	 **3c**	60
3	 **2d**	 **3d**	90
4	 **2e**	 **3e**	55
5[d]	 **2f**	 **3f**	70
6[d]	 **2g**	 **3g**	65
7[d]	 **2h**	 **3h**	45
8	 **2i**	 **3i**	90
9	 **2j**	 **3j**	85
10	 **2k**	 **3k**	75
11	 **2l**	 **3l**	85

[a] General reaction conditions: **1a** (4 mmol), **2** (1 mmol), Pd catalyst (2.5 mol%), **L7** (5 mol%), Na_2CO_3 (0.5 mmol), toluene (3 mL), 140°C, 20 h. [b] Yield of the isolated product. [c] The reaction was carried out at 120°C for 10 h. [d] The reaction was carried out with **L10** (5 mol%) and Na_2CO_3 (1 mmol) in *n*-heptane (5 mL).

Table 3: Palladium-catalyzed hydroamidation of 1,3-dienes and vinyl pyridines with **2a** and **2b**.[a]



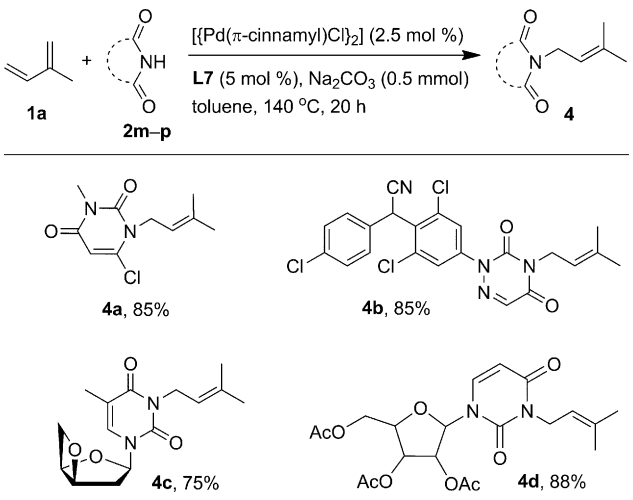
Entry	Diene or vinyl arene **1**	Product **3**	Yield [%][b]
1[c,d]			45
2[c]			52
3			50
4[d]			90
5			66
6[c]			70
7[c]			65
8[d]			80
9[d]			90
10			87
11			50

[a] General reaction conditions: **1** (1 mmol), **2** (1 mmol), Pd catalyst (2.5 mol%), **L7** (5 mol%), Na_2CO_3 (0.5 mmol), toluene (3 mL), 140°C, 20 h. [b] Yield of the isolated product. [c] The reaction was carried out with the palladium catalyst (7.5 mol%), **L7** (15 mol%), and Na_2CO_3 (1.5 mmol). [d] The reaction was carried out with 3.0 equivalents of the diene and Na_2CO_3 (1 mmol).

reaction was monitored in situ by ^{1}H NMR spectroscopy (see the Supporting Information for details). The reaction of the π-allyl Pd complex led to the formation of 1-cinnamyl-4-methylphthalimide **7** in high yield (70%; see Scheme S2 in the Supporting Information). Notably, no branched isomer was observed in the ^{1}H NMR spectrum. Furthermore, the reaction of [(dppp)Pd(π-cinnamyl)Cl] with isoprene and **2a** gave the desired 1,4-hydroamidation product in 70% yield as a single regioisomer (Table 1, entry 21).

We propose that the catalytic cycle for the regioselective 1,4-hydroamidation involves the initial formation of a transient Pd–H species, followed by reaction with the diene to give a cationic intermediate π-allyl Pd complex (see Scheme S3.) The backside nucleophilic attack of the imide to the less-substituted carbon atom explains the regioselective formation of the 1,4-hydroamidation product **3b** (see the Supporting Information for details).

Finally, having demonstrated the general reactivity of different substituted dienes with a variety of functionalized electron-poor N-heterocycles, amides, and sulfonamides, we were interested in using functionalized biologically important substrates, such as uracil, diclazuril, uridine, and thymidine derivatives. Interestingly, the reaction of **1a** with biologically relevant 6-chloro-1-methyluracil (**2m**), led to a single regioisomer **4a** in 85% yield (Scheme 3).[14] While diclazuril is known to be a potent coccidiocidal drug for the modern poultry industry,[15] uridine and thymidine are of key importance in biology as nucleobases of DNA and RNA. Derivatives of pyrimidine nucleobases have potential impact for the treatment of AIDS and cancer, and are widely applied as antitumor, antiviral, and antifungal drugs.[16,17]



Scheme 3. Palladium-catalyzed intermolecular hydroamidation of uracil, diclazuril, thymidine, and uridine derivatives.

Indeed, the reaction of isoprene (**1a**) with diclazuril (**2n**) provided **4b** as a single isomer in 85% yield. In a similar manner, thymidine and uridine derivatives were converted into the *N*-allylated thymidine and uridine derivatives **4c**–**4d** in 75–88% yield (Scheme 3). Notably, the catalytic protocol showed excellent tolerance towards the sensitive acetyl and nitrile groups and also the sugar moiety in these compounds.

In conclusion, we have reported a general intermolecular hydroamidation protocol for the transformation of electron-poor amides, imides, and sulfonamides with a series of 1,3-dienes and vinyl pyridines. This catalytic protocol facilitates

the synthesis of a variety of allylic amides. The reaction proceeds with high regioselectivity and shows good tolerance towards functional groups, as demonstrated by the functionalization of uracil and diclazuril as well as uridine and thymidine derivatives. Notably, the resulting allylic amines are important bioactive pharmaceuticals and intermediates in the chemical industry.[18]

Experimental Section

Under an Ar atmosphere, an oven-dried pressure tube was charged with 4-methylphthalimide (**2a**, 1 mmol). The Pd catalyst (2.5 mol%), **L7** (5 mol%), and the base (0.5 mmol) were added one by one, followed by toluene (3 mL), a magnetic stirrer bar, and isoprene (**1a**, 4 mmol). The reaction mixture was stirred at 120°C for 10 h and then cooled to room temperature, diluted with ethyl acetate (10 mL), and dried over anhydrous Na_2SO_4. The filtrate was concentrated under reduced pressure, and the residue was purified by silica-gel column chromatography with ethyl acetate/hexane as the eluent to afford **3a** (80%) as a colorless oil.

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