Dearomative Addition-Hydrogen Auto-Transfer for Branch-Selective *N*-Heteroaryl C-H Functionalization via Ruthenium-Catalyzed C-C Couplings of Diene Pronucleophiles

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ABSTRACT: A novel mechanism for *N*-heteroaryl C-H functionalization via dearomative addition-hydrogen auto-transfer is described. Upon exposure to the catalyst derived from $RuHCl(CO)(PPh_3)_3$ and Xantphos, dienes **1a**-**1g** suffer hydroruthenation to form allylruthenium nucleophiles that engage in *N*-heteroaryl addition-β-hydride elimination to furnish branched products of C-C coupling **3a**-**3s** and **4a**-**4f**. Oxidative cleavage of isoprene adducts **3j**, **3k**, **3l** and **3n** followed by ruthenium-catalyzed dynamic kinetic asymmetric ketone reduction provides enantiomerically enriched *N*-heteroarylethyl alcohols **6a**-**6d** and, therefrom, *N*-heteroarylethyl amines **7a**-**7d**. DFT calculations correlate experimentally observed regioselectivities with the magnitude of the *N*-heteroaryl LUMO coefficients and corroborate rate-determining dearomative allylruthenium addition. In the presence of 2-propanol and trifluoroethanol, dearomatized adducts derived from pyrimidine **2a** and quinazoline **2n** were isolated and characterized.

Introduction

Aromatic *N*-heterocycles are ubiquitous substructures among small molecule drugs.[1] Yet despite 30 years following Murai's initial report of aryl C-H alkylation via directed C-H oxidative-alkene insertion,[2] branch-selective variants that are applicable to diverse 5- and 6-membered *N*-heterocycles remain elusive.[3,4] In pioneering work by Nakao and Hiyama,[5a-c] Lewis acids were found to unlock Murai-type reactions of pyridines by simultaneously activating the C-H bond toward oxidative addition and masking the Lewis basic pyridine nitrogen atom, which otherwise can impede catalysis via coordinative saturation of the metal. However, these processes require pyrophoric trialkyl aluminum-based Lewis acids and expansion to heteroaryl partners beyond pyridine are scant.[5] An alternate strategy for C-H alkylation of *N*-heterocycles potentially involves dearomative addition to the azine C=N bond followed by rearomatization.[6] To our knowledge, intermolecular metal-catalyzed dearomative addition of π-unsaturated pronucleophiles to unmodified aromatic *N*-heterocycles are limited to copper-catalyzed processes,[7] for example, 1,4-additions to pyridines and pyridazines, which require rearomatization by treatment with air or H_2O_2[7a] and additions to the C2-position of benzimidazoles.[7b,c] Here, using diene pronucleophiles, we report the first ruthenium-catalyzed *N*-heteroaryl C-H functionalizations via dearomative addition-hydrogen auto-transfer,[8,9,10] which are applicable to diverse electron-deficient aromatic *N*-heterocycles. Additionally, we report conversion of the reaction products to enantiomerically enriched *N*-heteroarylethyl alcohols and amines via dynamic kinetic asymmetric ketone reduction (Figure 1).[11]

Results and Discussion

Given the surprisingly low resonance stabilization energy of pyrimidines (8 kcal/mol),[12] couplings to methyl pyrimidine-5-carboxylate **2a** were initially explored. As identification of optimal conditions required extensive variation of reaction parameters, a concise summary of key experiments are highlighted by deviation from optimal conditions, which involved exposure of methyl pyrimidine-5-carboxylate **2a** (100 mol%) and isoprene **1a** (400 mol%) to the catalyst derived from $RuHCl(CO)(PPh_3)_3$ (5 mol%) and xantphos[13] (5 mol%) in toluene solvent (1 M) at 100 ºC (Table 1).[14] Under these conditions, a 93% yield of adduct **3a** was obtained (Table 1, entry 1). Reactions using alternate chelating phosphine ligands displayed diminish catalytic activity (Table 1, entries 2-3). Precatalysts commonly used in Murai-type C-H functionalizations[2,3] failed to animate the catalytic process (Table 1, entries

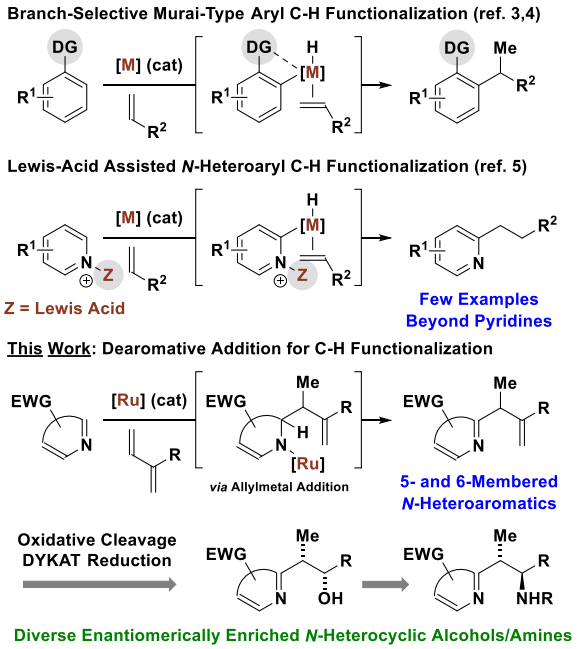
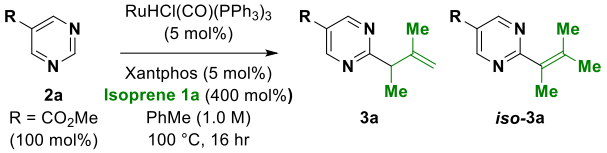


Figure 1. Branch-Selective Aryl C-H Functionalization.

Table 1. Ruthenium-catalyzed hydroarylation of isoprene **1a** with pyrimidine **2a**: Deviation from optimal conditions.[a]



Entry	*Deviation from Optimal Conditions*	**3a** Yield (%)	**3a**:*iso*-**3a**
➡ **1**	**None**	**93**	**>20:1**
2	(*S*)-BINAP as Ligand	82 (47% ee)	>20:1
3	Dppf as Ligand	54	>20:1
4	Without Ligand	21	>20:1
5	$Ru_3(CO)_{12}$	<5	---
6	$[RuCl_2(cymene)]_2$	<5	---
7	$RuH_2(CO)(PPh_3)_3$	27	9:1
8	115 °C	95	7:1
9	36 hr	98	<1:20
➡ **10**	**1 mol% Catalyst 2.5 Gram Scale**	**96**	**>20:1**

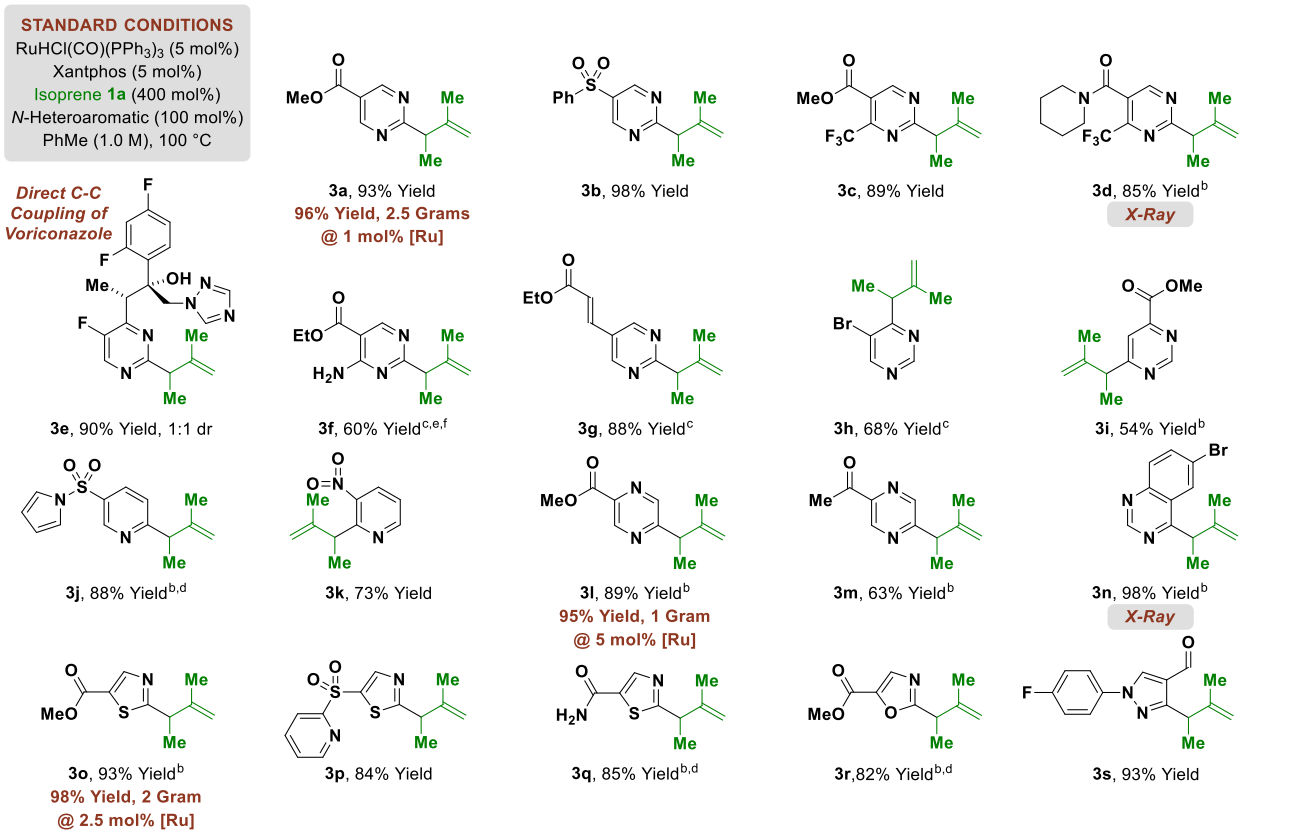
[a]Yields are of isomeric mixtures isolated by silica gel chromatography. See Supporting Information for further experimental details.

5-7). At higher temperatures partial isomerization of the initially formed adduct **3a** to the conjugated heteroaromatic *iso*-**3a** is observed (Table 1, entry 8) and, at longer reaction times, complete conversion to *iso*-**3a** is evident (Table 1, entry 9). Such isomerization also occurs upon reexposure of **3a** to the reaction conditions. The highly efficient nature of this catalytic process is underscored by the formation of **3a** on 2.5 gram scale at low catalyst loading (1 mol%) in 96% yield (Table 1, entry 10).

To assess reaction scope, optimal conditions developed for transformation of isoprene **1a** and methyl pyrimidine-5-carboxylate **2a** to adduct **3a** were applied to aromatic *N*-heterocycles **2b**-**2s** (Table 2). As illustrated by the formation of adducts **3a**-**3i**, diverse pyrimidines **2a**-**2i** participate in this process. When the pyrimidine nucleus is substituted at the 5-position, C-C coupling usually occurs at the C2 position. However, as demonstrated by the reaction of 5-bromopyridimine **2h**, coupling at C4 also can occur, and for methyl pyrimidine-4-carboxylate **2i**, C-C coupling occurs at C6. High chemoselectivity is highlighted by the direct modification of voriconazole **2e**, which provides adduct **3e** in 90% yield, demonstrating the relevance of this method *vis-à-vis* late-stage functionalization of drug candidates.[15] Beyond pyrimidines **2a**-**2i**, pyridines **2j** and **2k**, pyrazines **2l** and **2m**, quinazoline **2n**, thiazoles **2o**, **2p**, and **2q**, oxazole **2r**, and pyrazole **2s**, all participate in efficient C-C coupling to isoprene. In all cases, single regioisomers were observed. As will be described (*vide infra*), regioselectivities correlate with the magnitude of the calculated LUMO coefficient.

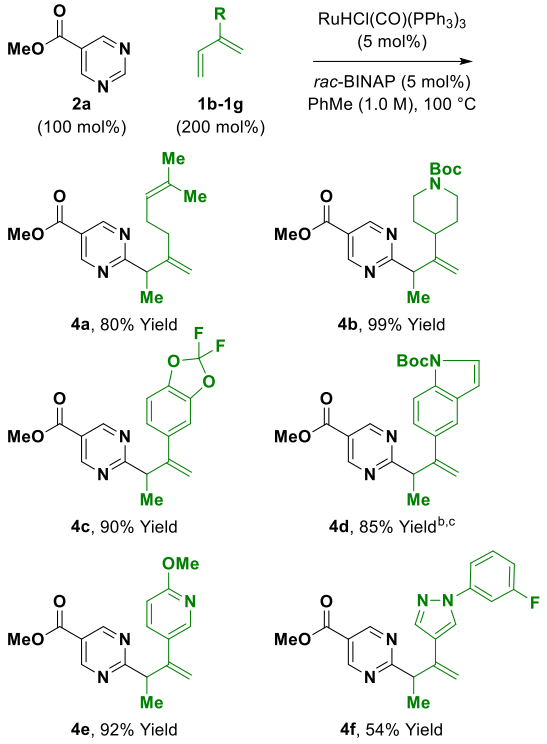
In a further illustration of reaction scope, 2-substituted dienes **1b**-**1g** beyond isoprene **1a** were briefly investigated in couplings to methyl pyrimidine-5-carboxylate **2a** under standard reaction conditions but using *rac*-BINAP as ligand (Scheme 1). As demonstrated by the formation of adducts **4a** and **4b**, which are derived from myrcene **1b** and **1c** *N*-Boc 4-(1,3-butadienyl)piperidine, 2-substituted butadienes bearing olefin side chains and saturated *N*-heterocycles are competent partners for C-C coupling. Adducts **4c** and **4d** incorporate

Table 2. Ruthenium-catalyzed dearomative addition-hydrogen auto-transfer reactions of isoprene **1a** with *N*-heterocycles **2a**-**2s**.[a]



[a]Yields are of material isolated by silica gel chromatography. [b]115 ºC. [c]130 ºC. [d]48 hr. [e]PhMe (2.0 M). [f]$RuHCl(CO)(PPh_3)_3$ (10 mol%), Xantphos (10 mol%). See Supporting Information for further experimental details.

Scheme 1. Ruthenium-catalyzed dearomative addition-hydrogen auto-transfer reactions of dienes **1b-1g** with methyl pyrimidine-5-carboxylate **2a**.[a]

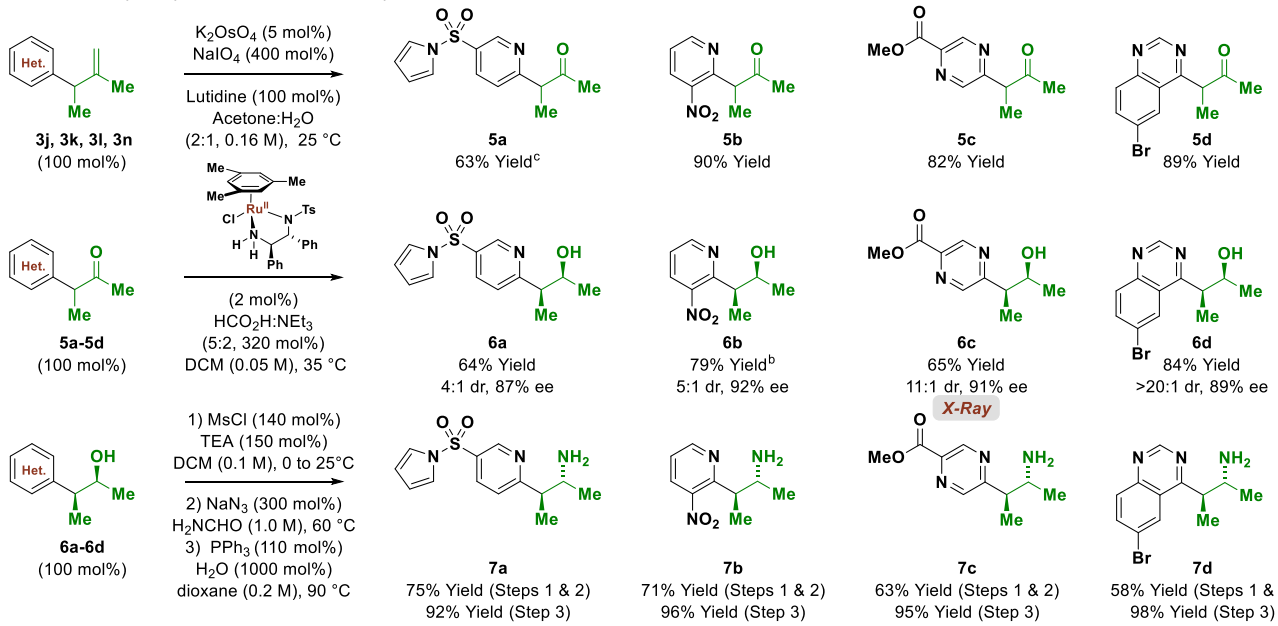


[a]Yields are of material isolated by silica gel chromatography. [b]115 ºC. [c]Xantphos (5 mol%). See Supporting Information for further experimental details.

5-(2,2-difluorobenzo)-1,3-dioxole and indole moieties, respectively. Finally, the formation of **4e** and **4f** highlight chemoselective modification of the C2 carbon of methyl pyrimidine-5-carboxylate **2a** in the presence of 5-(2-methoxypyridyl) and 4-(*N*-fluorophenyl)pyrazoyl groups. Under the present conditions, butadiene or 1,2-propadiene (allene) provide mixtures of non-conjugated and conjugated adducts, whereas 1-phenyl-1,3-butadiene did not participate in coupling.

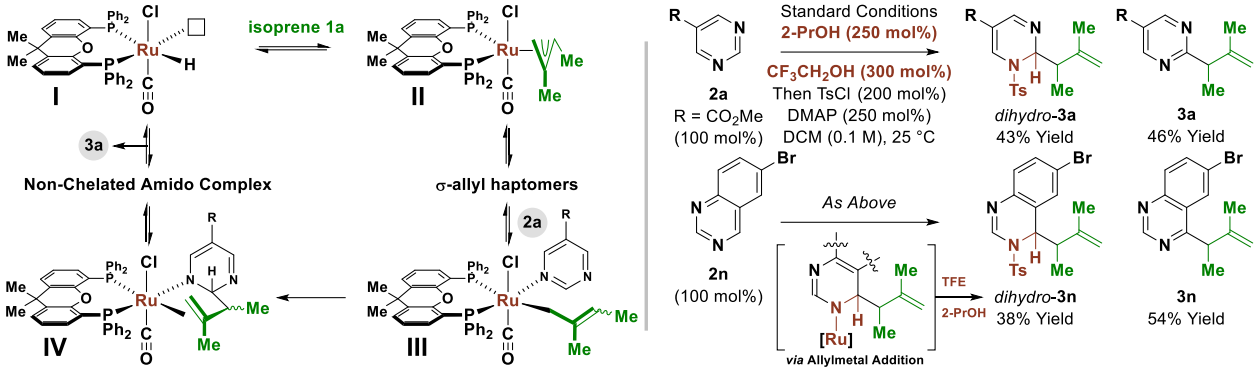
The utility of the present *N*-heteroaryl-containing isoprene adducts **3a-3s** is demonstrated by the conversion of representative adducts **3j**, **3k**, **3l** and **3n** to the corresponding enantiomerically enriched *N*-heteroarylethyl alcohols **6a-6d** and *N*-heteroarylethyl amines **7a-7d** (Scheme 2). Johnson-Lemieux oxidative cleavage[16] of isoprene adducts **3j**, **3k**, **3l** and **3n** provided *N*-heteroaryl ketones **5a-5d**, respectively. As ketones **5a-5d** are isoelectronic with β-dicarbonyl and susceptible to epimerization under mild conditions, their dynamic kinetic asymmetric reduction mediated by formic acid was attempted using a small set of Noyori-type η^6-arene complexes bearing *N*-arylsulfonyl ligands derived from 1,2-diphenyl ethylene diamine (DPEN).[12,17] The indicated catalyst derived from mesitylene and (*R*,*R*)-TsDPEN proved to be most selective, providing the *N*-heteroarylethyl alcohols **6a-6d** with good levels of *syn*-diastereo- and enantioselectivity. The relative and absolute stereochemical assignment of alcohols **6a-6d** were made in analogy to that determined for alcohol **6c**, which was established via single crystal X-ray diffraction. Mesylation of alcohols **6a-6d** followed by treatment with sodium azide in formamide solvent (which suppressed elimination)[18] provided the corresponding homobenzylic azides, which upon Staudinger reduction[19] delivered the hitherto unknown *N*-heteroarylethyl amines **7a-7d** in enantiomerically enriched form as single diastereomers.

Scheme 2. Oxidative cleavage of adducts **3j**, **3k**, **3l** and **3n** and conversion to enantiomerically enriched *N*-heteroarylethyl alcohols **6a-6d** and *N*-heteroarylethyl amines **7a-7d** via dynamic kinetic resolution.[a]



[a]Yields are of material isolated by silica gel chromatography. Diastereo- and enantioselectivities were determined by chiral stationary phase HPLC analysis. [b]THF (0.05 M). [c]$NaIO_4$ (300 mol%). Enantioselectivities correspond to the *syn*-diastereomers. See Supporting Information for further experimental details.

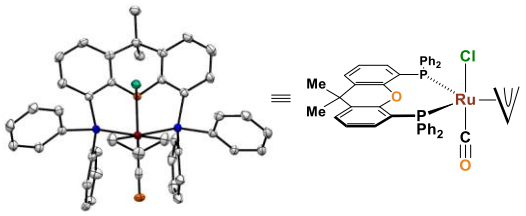
Scheme 3. Proposed catalytic cycle and capture of putative dearomatized adducts derived from pyrimidine **2a** and quinazoline **2n**.[a]



[a]Yields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details.

A catalytic cycle for the ruthenium-catalyzed C-C coupling of *N*-heterocycles with isoprene has been proposed wherein diene hydroruthenation[20] delivers an allylruthenium nucleophile **II** that engages in C=N addition-β-hydride elimination (Scheme 3). To corroborate the indicated mechanism, an attempt was made to intercept the putative dearomatized intermediate **IV** derived from pyrimidine **2a** and quinazoline **2n** via protonolytic cleavage of the Ru-N bond of **IV** by conducting the reaction in the presence of 2-propanol and CF_3CH_2OH (TFE).[21] Although β-hydride elimination from the amidoruthenium intermediate **IV** might be anticipated to be rapid as it reestablishes aromaticity, chelation by the homoallylic olefin should retard the rate of β-hydride elimination via coordinative saturation of the metal center. Indeed, related ruthenium-catalyzed C-C couplings of butadiene or isoprene with carbonyl electrophiles form homoallylic alcohols and not β,γ-unsaturated ketones.[22] Thus, transfer hydrogenolysis or protonolysis of the Ru-N bond in **IV** by 2-propanol or TFE may occur at a rate comparable to β-hydride elimination. In the event, exposure of pyrimidine **2a** and quinazoline **2n** to isoprene in the presence of 2-propanol and TFE under standard reaction conditions followed by introduction of *p*-toluenesulfonyl chloride and DMAP enabled isolation of the dearomatized sulfonamides *dihydro*-**3a** and *dihydro*-**3n** in 43% and 38% yields, respectively. Notably, exposure of the

Figure 2. Structure of RuCl(CO)[η^3-C_3H_5][Xantphos] determined by single crystal X-ray diffraction.[a]

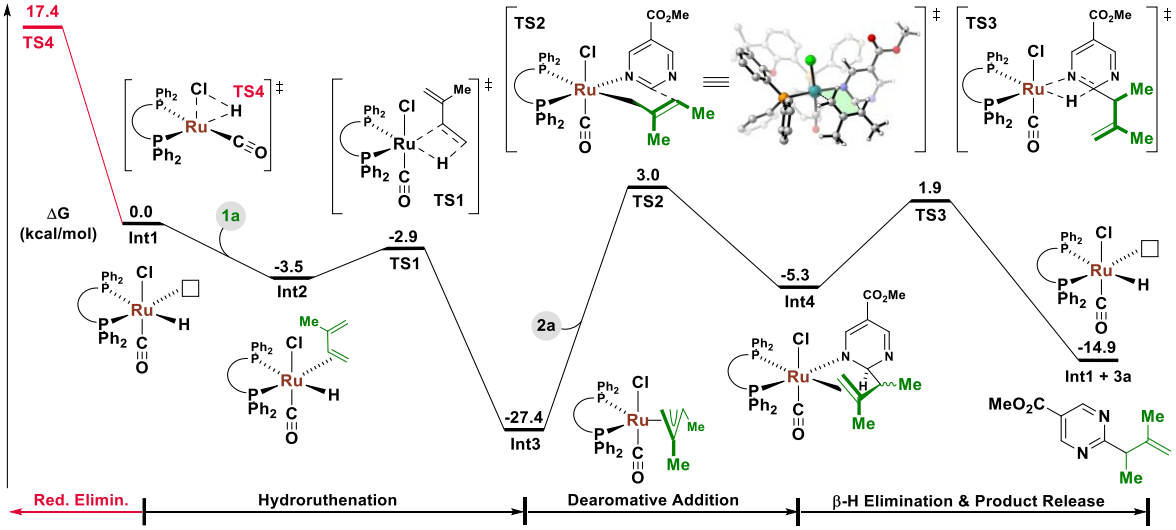


[a]See Supporting Information for crystallographic data.

aromatic products **3a** and **3n** to 2-propanol and TFE under standard conditions did not result in the formation of *dihydro*-**3a** and *dihydro*-**3n**, suggesting *dihydro*-**3a** and *dihydro*-**3n** do not arise via reduction of **3a** and **3n**, but are generated via interception of the amidoruthenium intermediate **IV**.

At this stage, density functional theory (DFT) calculations informed by X-ray crystallographic data for RuCl(CO)[η^3-C_3H_5][XantPhos] (Figure 2) were undertaken to assess the feasibility of the dearomative addition pathway (Figure 3). The 16-electron Ru hydride **Int1** binds to isoprene **1a** to form coordinatively saturated **Int2**. The isoprene hydrometallation[20] occurs with a very low barrier of only 0.6 kcal/mol *via* **TS1** to

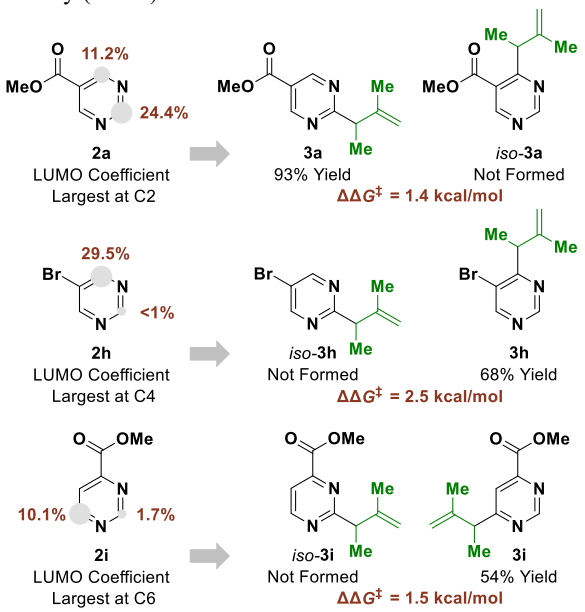
Figure 3. Computed reaction energy profiles for ruthenium-catalyzed *N*-hetereoaryl C-H *sec*-prenylation via dearomative addition.[a]



[a]DFT calculations were performed at the M06/SDD–6-311+G(d,p)/SMD(PhMe)//B3LYP-D3(BJ)/LANL2DZ–6-31G(d) level of theory. See Supporting Information for further details.

form π-allyl complex **Int3**, which is in equilibrium with its σ-allyl haptomers (not shown).[23] Coordination of methyl pyrimidine-5-carboxylate **2a** triggers dearomative addition through a Zimmerman–Traxler-type transition state (**TS2**) giving rise to the chelated amidoruthenium species **Int4**. Subsequent β-hydride elimination (**TS3**) releases the C-H *sec*-prenylation product **3a** and regenerates ruthenium hydride **Int1**. The transition state for dearomative addition (**TS2**) was found to be rate-determining (30.4 kcal/mol with respect to the π-allyl complex **Int3**). As Murai-type reactions proceed via C-H bond oxidative addition by zero-valent ruthenium complexes,[3] the transition state for reductive elimination of HCl (**TS4**) from **Int1** to afford a zero-valent ruthenium species was computed and found to be much less favorable than the hydroruthenation–dearomative addition pathway. Finally, if the proposed reaction mechanism is indeed operative and dearomative addition represents the rate- and selectivity determining step, the regioselectivity of C-C coupling should track with the magnitude of the heteroarene LUMO coefficient. Hence, LUMO coefficients for pyrimidines **2a**, **2h**, and **2i**, which display divergent regioselectivity at C2, C4, and C6, respectively, were calculated and compared to the observed regioselectivities (Figure 4). In each case, the observed regioselectivities correlated with the positions at which the LUMO coefficients were largest. The small difference between the calculated energies and experimental selectivities is common and falls within the error of DFT calculations.

Figure 4. Correlation of observed regioselectivity with magnitude of the calculated LUMO coefficients and DFT-computed selectivity ($\Delta\Delta G^{\ddagger}$) in dearomative addition.[a]



[a]See Supporting Information for further details.

In summary, we report the first ruthenium-catalyzed *N*-heteroaryl C-H functionalizations via dearomative addition-hydrogen auto-transfer of diene pronucleophiles. Reaction scope is broad, encompassing both 5- and 6-membered aromatic *N*-heterocycles **2a**-**2s**, as well as dienes **1a**-**1g**. The collective experimental and computational data corroborate a catalytic cycle in which diene hydrometalation delivers an allylruthenium nucleophile, which engages in rate-determining *N*-heteroaryl addition at the carbon atom possessing the largest LUMO coefficient. Subsequent β-hydride elimination provides branched adducts and closes the catalytic cycle. As demonstrated by the formation of compounds **6a**-**6d** and **7a**-**7d**, this method unlocks entry to diverse enantiomerically enriched *N*-heteroarylethyl alcohols and *N*-heteroarylethyl amines, respectively. Future studies are aimed at the development of related aryl C-H functionalizations that operate via dearomative addition, including enantioselective (α-aryl)allylations mediated by arylpropyne pronucleophiles.[21]

Supporting Information. Experimental procedures and spectroscopic data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS), including images of NMR spectra. Single-crystal X-ray diffraction data for compounds **3d**, **3n**, **6c**-OBz and RuCl(CO)[η^3-C_3H_5][Xantphos].

Accession Codes. CCDC 2366333 (**3d**), 2367430 (**3n**), 2380419 {RuCl(CO)[η^3-C_3H_5][Xantphos]} and 2380418 (**6c**-OBz) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes
The authors declare no competing financial interest.

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