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Chemoselectivity for Alkene Cleavage by Palladium-Catalyzed Intramolecular Diazo Group Transfer from Azide to Alkene

Grant B. Frost, Michaela K. Mittelstaedt and Christopher J. Douglas*

Dedicated to all organic azide chemists

Abstract: Alkenes can be cleaved via the (3+2) cycloaddition and subsequent cycloreversion of 1,3-dipoles, classically ozone (O_3), but the azide (R–N_3) variant is rare. Chemoselectivity for these azide to alkene diazo group transfers (DGT) is typically disfavored, thus limiting their synthetic utility. Herein, we disclose a palladium-catalyzed intramolecular azide to alkene DGT, which grants chemoselectivity over competing aziridination. Our data support a catalytic cycloreversion mechanism distinct from other known metal-catalyzed azide/alkene reactions: nitrenoid/metalloradical and (3+2) cycloadditions. Kinetics experiments reveal an unusual mechanistic profile in which the catalyst is not operative during the rate-controlling step, rather, it is active during the product-determining step. Catalytic DGT was used to synthesize N-heterocyclic quinazolinones, a medicinally relevant structural core. We also report on the competing aziridination and subsequent ring expansion to another N-heterocyclic core structure of interest, benzodiazepinones.

Nitrogen is found extensively in organic molecules: natural products, pharmaceuticals, and materials. Thus, the construction of C–N bonds is a continual core goal of synthetic organic chemists. Organic azide (R–N_3) reactions are a common strategy for incorporating nitrogen into target molecules of various sizes and complexities. This broad utility is due to the immense diversity of azide reactivity: 1,3 dipole, nitrene, nucleophile, electrophile, and radical.[1] Although this grants organic azides synthetic versatility, it also necessitates the development of methods to control selectivity. In the context of thermolytic azide/alkene reactions, the chemoselectivity challenge is two-fold (**Scheme 1**, **a**, **top**). There is an initial divergence of mechanistic paths: nitrene formation versus (3+2) cycloaddition. Nitrenes often react with alkenes to form aziridines, but are so energetic they tend to indiscriminately aminate at C–H bonds as well.[2] (3+2) cycloadditions form triazolines, some of which are isolable, but most rearrange to form imines and aziridines with the expulsion of N_2.[3] However, Huisgen et al. observed that triazolines can also rearrange via N–N bond cleavage,[4] and Fusco et al. discovered that both N–N and C–C bond cleavage can occur.[5] Regitz et al. categorized these mechanisms as azide to alkene DGT, as imines and diazos (R–N_2) result.[6] This is analogous to alkene ozonolysis in which a carbonyl and carbonyl oxide (R–O_2) form. However, cleavage of the alkene C–C bond subsequent to azide (3+2)

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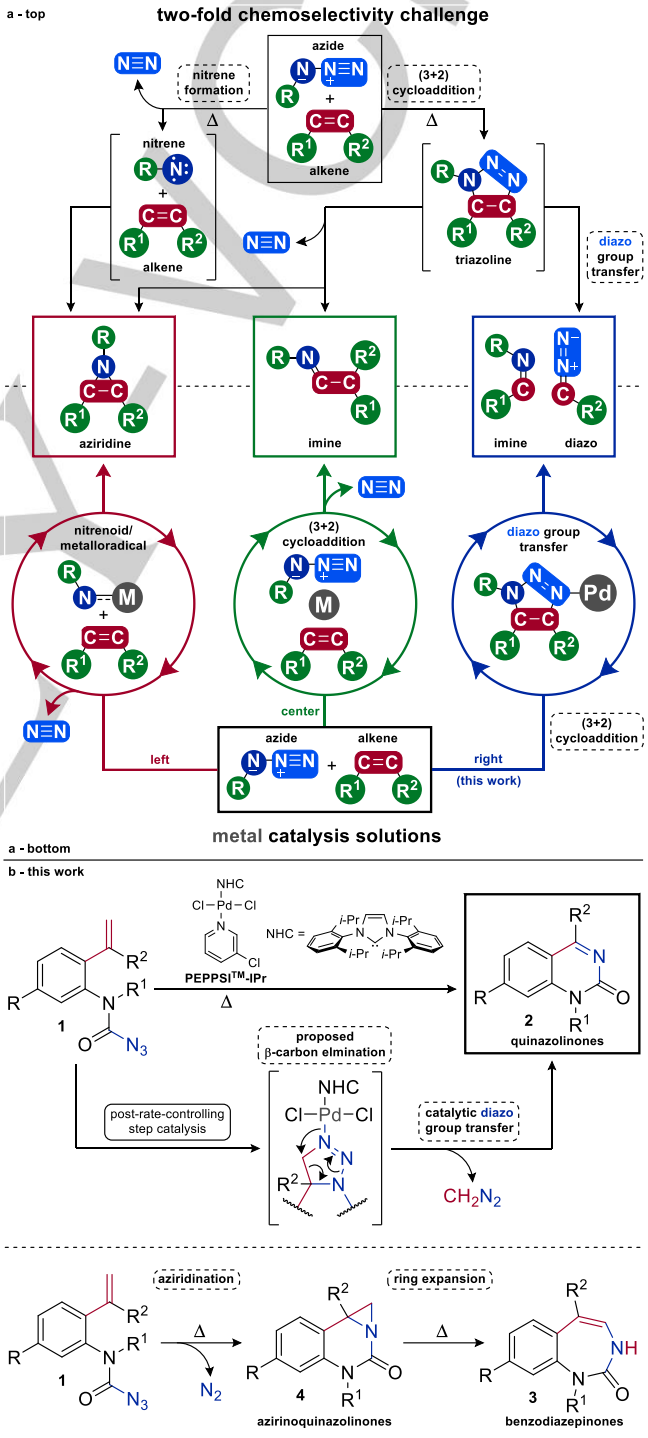

Scheme 1. Chemoselectivity challenge of azide/alkene reactions, metal catalysis solutions and this work

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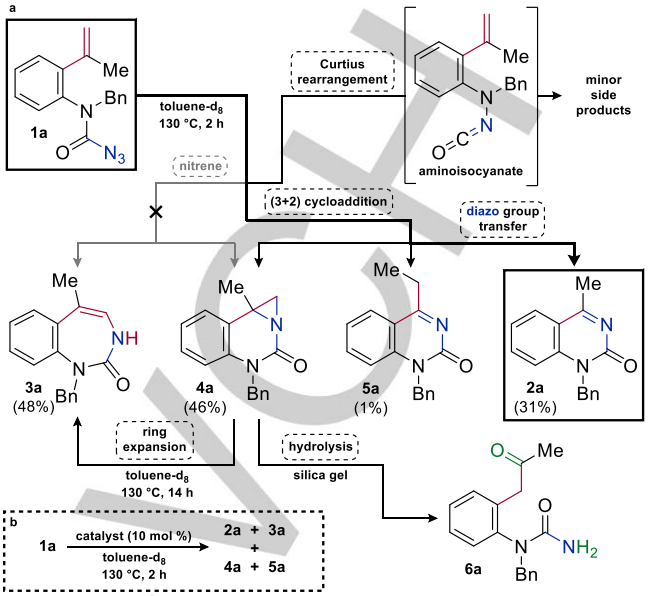
cycloaddition is usually disfavored, in contrast to the ozonolysis of C–C bonds. Chemoselectivity for azide to alkene DGT with C–C bond cleavage has thus far been based solely on substituent effects. DGT may be favored over other pathways with sufficiently electron poor azide diazo donors (R = SO_2R^3 or $POR^3{}_2$) and electron rich alkene diazo acceptors (R^1 = N or O).[6a,7] Catalyst-based chemoselectivity for DGT is desirable, as it could allow for reactivity comparable to ozonolysis, but with the incorporation of nitrogen into the products, namely imines and potentially synthetically versatile diazos.

Significant strides have been made in controlling the chemoselectivity of azide/alkene reactivity with metal catalysts (**Scheme 1**, **a**, **bottom**). It is well established that catalysts (M = Co, Fe, Ru, Rh) can selectively cleave azides to nitrenoids/metalloradicals and impose control for aziridination **(Scheme 1**, **a**, **left**).[8] Although a vast amount of research has been aimed at metal-catalyzed azide/alkyne (3+2) cycloadditions (M = Cu, Ru, Ag),[9] there are few reports of metal-catalyzed azide/alkene (3+2) cycloaddition reactions. Rare earth metals, Ce and Sm, are thought to catalyze cycloadditions with subsequent decomposition of the triazolines to imines (**Scheme 1**, **center**).[10] Pd^{II}-catalysts can also affect azide/alkene reactivity, however it is unclear if there is a consistent mechanism involved. Migita et al. reported the $PdCl_2(PhCN)_2$-catalyzed allylic ether isomerization with subsequent azide cycloaddition and rearrangement to imines.[11] Recently, Ramasastry et al. reported $Pd(OAc)_2$ altered the chemoselectivity of a thermal azide/alkene ring closing reaction to form the pyridine ring of β-carbolines.[12] However, all of these transformations involve only the expulsion of N_2. Herein we report a Pd^{II}-catalyzed cycloreversion to achieve azide to alkene DGT with C–C bond cleavage (**Scheme 1**, **right**).

We centered our studies of catalytic azide to alkene DGT on the reactions of carbamoyl azides **1** with Pd^{II}-complex PEPPSI™-IPr. (**Scheme 1**, **b**). The kinetics of catalytic DGT are fascinating in that the reaction is overall zeroth order in Pd, indicating that the catalyst effects the product-determining step and not the rate-controlling step. Based on our evidence and literature precedence we propose the plausible key mechanistic step to be a Pd^{II}-promoted β-carbon elimination/cycloreversion from an intermediate cycloadduct. Through this, we chemoselectively synthesized quinazolinones **2**. Under noncatalyzed thermolytic conditions we synthesized benzodiazepinones **3** via the ring expansion of azirinoquinazolinones **4**. Our synthetic focus was in accordance with the noteworthy strategy of employing azide/alkene cycloadditions/rearrangements for the synthesis of other N-heterocyclic targets.[12-13] Both quinazolinones and benzodiazepinones are core structures of many bioactive molecules of interest and new methods for their construction are continually sought.[14]

Our studies commenced with heating a solution of **1a** in toluene-d_8 to 130 °C in an NMR tube. (**Table 1**, **a**, entry 1). We were initially not hypothesizing any of the DGT product **2a** to form as this was neither a sulfonyl/phosphoryl azide nor an enamine/enol ether reaction. Nor were we expecting enamine product **3a** as this would appear to indicate an unlikely vinylic C–H nitrene amination. A thermolytic Curtius rearrangement of an acyl azide should be a concerted process that does not involve an intermediate nitrene.[15] However, after 14 hours **1a** was fully

Table 1. Thermolysis reaction and catalyst optimization



entry	catalyst	2a[a]	3a	4a	5a
1	none[b]	29%	48%	<1%	1%
2	none	31%	<1%	46%	1%
3	$PdCl_2(PhCN)_2$	19%	27%	1%	10%
4	$Pd(OAc)_2$	16%	27%	6%	9%
5	$PdCl_2$	27%	20%	17%	4%
6	$PdCl_2(PPh_3)_2$	54%	2%	10%	4%
7	**PEPPSI™-IPr**	**68%**	**1%**	**5%**	**5%**
8	PEPPSI™-IPr[c]	59%	2%	6%	4%
9	PEPPSI™-IPr[d]	62%	1%	6%	3%

[a] product yields. [b] time = 14 hours [c] 5 mol % [d] 20 mol %

consumed and surprisingly, a mixture of primarily **2a** (29%) and **3a** (48%) was observed with quantitative ^{1}H NMR (qNMR) along with a very minor quantity of imine **5a** (**Table 1**, entry 1). Formation of **2a** could be rationalized as the carbamoyl azide is still an electron poor diazo group donor and the alkene is ortho to the secondary aniline and therefore could still serve as a relatively electron rich diazo acceptor. Rationale for the formation of **3a** remained elusive.

Next, we reacted **1a** for just 2 hours and in this case **1a** was already 94% consumed, and a mixture of **2a** (31%) and aziridine **4a** (46%) was obtained (**Table 1**, entry 2). Since an approximately equimolar quantity of **4a** formed prior to **3a** we proposed that **3a** results from the ring expansion of **4a**. Indeed, Woerner et. al. reported a single example of an analogous thermal aziridine ring expansion.[16] Subsequent attempts to isolate **4a** with silica gel column chromatography were unsuccessful. Instead, we isolated urea **6a**, a plausible hydrolysis product (see supporting information).[17] Thus, our structural assignment of **4a** as the azirinoquinazolinone was predicated on both the observed ring expansion to **3a**, as well as the isolation of **6a**. Also, the overall mass balance of identifiable products was non-ideal, thus we hypothesized a Curtius rearrangement was diverting a minor portion of **1a** to unidentified side products (see supporting information).[18]

With the relevant products of the thermolysis reaction identified we began testing Pd^{II} catalysts for their effect on chemoselectivity (**Table 1**, **b**). $PdCl_2(PhCN)_2$ (Migita's

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conditions)[11] altered the product distribution significantly, decreasing **2a** and promoting formation of **3a** from **4a** or producing **3a** via an alternative mechanism (**Table 1**, entry 3). Interestingly, the yield of **5a** also increased considerably. $Pd(OAc)_2$, (Ramasastry's conditions)[12] produced a similar product distribution to $PdCl_2(PhCN)_2$ (**Table 1**, entry 4). $PdCl_2$ improved the mass balance compared to the first two Pd^{II} catalysts (**Table 1**, entry 5). However, no significant chemoselectivity was achieved with the initial entries. $PdCl_2(PPh_3)_2$ was selective for DGT, producing **2a** in 54% yield, favoring it over the aziridination/ring expansion pathway 4.5:1 (**2a**:(**3a** + **4a**)) (**Table 1**, entry 6). PEPPSI™-IPr improved the yield and chemoselectivity for **2a** (68%, 11.3:1) (**Table 1**, entry 7). Altering the loading of PEPPSI™-IPr to 5% and 20% each decreased the yield and selectivity slightly (**Table 1**, entries 8-9).

We performed reaction progress kinetics with qNMR to assess the general kinetic behavior of these unique catalytic and thermolytic reactions (**Figure 1**). The PEPPSI™-IPr-catalyzed and the thermolysis reactions were monitored until maximum yields of **2a** were observed. This occurred between 120 and 150 minutes for both reactions, at ~95-97% conversion of **1a**, as we observed a minor degradation of **2a** at further time points. The plot illustrates the stark chemoselectivity achieved with PEPPSI™-IPr, but interestingly we did not observe a change in the rate of **1a** consumption. Rather, the rate of **2a** formation drastically increased while the rate of **4a** formation decreased.

We expanded our kinetic analysis by performing a series of initial rate measurements. The initial rates of **1a** conversion for the thermolysis reaction ($\mathbf{v_{1a}}$) and the PEPPSI™-IPr reaction ($\mathbf{v_{1a(Pd)}}$) were approximately equal, as observed with reaction progress kinetics (**Table 2**, entries 1-2). Halving [PEPPSI™-IPr] produced an initial rate within error of $\mathbf{v_{1a}}$ and $\mathbf{v_{1a(Pd)}}$, supporting an overall zeroth order in Pd (**Table 2**, entry 3). The presence of catalyst only affected the initial rates of formation of **2a** ($\mathbf{v_{2a}}$) and **4a** ($\mathbf{v_{4a}}$). Halving [**1a**] resulted in an approximately two-fold reduction in $\mathbf{v_{1a(Pd)}}$, supporting an expected first order reaction in azide (**Table 2**, entry 4). We synthesized azide **7** with no alkene as a proxy for measuring the rate of the hypothesized Curtius rearrangement that may compete with productive (3+2) cycloaddition. The initial rate of conversion of **7** ($\mathbf{v_7}$) under thermolytic conditions was measured (**Table 2**, entry 5). Remarkably, the sum of $\mathbf{v_7}$ with the rates of product formation $\mathbf{v_{2a}}$ and $\mathbf{v_{4a}}$ was within error of $\mathbf{v_{1a}}$ (-2.64e-6 ± 1.16e-7 *M*/s ≈ -2.61e-6 ± 1.46e-7) This accounts for the full mass balance. When **7** was reacted in the presence of PEPPSI™-IPr the rate of conversion increased slightly (**Table 2**, entry 6). This may indicate that some nonproductive interaction of Pd and azide could occur prior to cycloaddition.

Next, we broadened our studies to other azide **1** substrates (**Scheme 2**). We first targeted derivatives substituted para to the alkene with groups of varying electronic character. Substrates **1b**-**1f** were subjected to both sets of reaction conditions. Yields were measured with qNMR at two timepoints (2 and 2.5 hours) to gauge if a significant change in rate or decomposition occurred. The duration of the thermolysis reactions was then extended (overnight) to observe the ring expansion of **4** to **3**. Strikingly, the chemoselectivity for the thermolysis of **1** was greatly influenced by the electronic character of the ring. More electron rich substrates **1b** and **1c** had decreased preference for DGT and

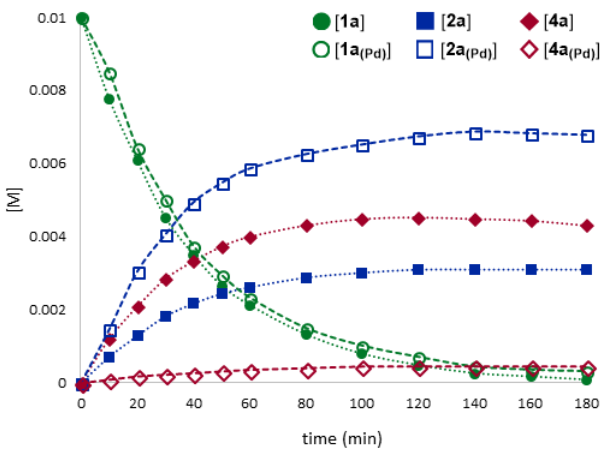
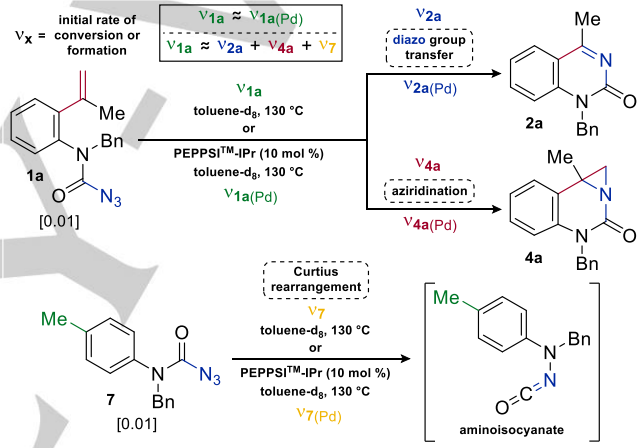


Figure 1. Reaction progress kinetics

Table 2. Initial rates kinetics experiments



entry	[**1a**]	[**Pd**]	$\mathbf{v_{1a}}$ (*M*/s)	$\mathbf{v_{2a}}$ (*M*/s)
1[a]	[0.01]	-	-2.61e-6 ± 1.46e-7	8.14e-7 ± 5.46e-8
2[b]	[0.01]	[0.001]	-2.51e-6 ± 7.90e-8	1.74e-6 ± 2.65e-7
3	[0.01]	[0.0005]	-2.59e-6 ± 5.77e-8	1.79e-6 ± 2.38e-7
4	[0.005]	[0.001]	-1.31e-6 ± 6.26e-8	9.63e-7 ± 5.52e-8
entry	[**7**]	[**Pd**]	$\mathbf{v_7}$ (*M*/s)	-
5	[0.01]	-	-5.42e-7 ± 3.24e-8	-
6	[0.01]	[0.001]	-6.89e-7 ± 3.21e-8	-

[a] $\mathbf{v_{4a}}$ = 1.28e-6 ± 9.70e-8 [b] $\mathbf{v_{4a(Pd)}}$ below detection threshold for Pd-catalyzed reactions

more electron poor substrates **1d**-**1f** had increased preference for DGT products. **1f**, the most electron poor substrate tested, favored DGT over aziridination 1.5:1. We established a Hammett linear free energy relationship (LFER) that illustrates this electronic bias for chemoselectivity (**Figure 2**). σ_{para} correlated very well with the observed chemoselectivity (R^2 = 0.99) and ρ = 0.68. Despite the increased electronic bias for aziridination with more electron rich substrates, PEPPSI™-IPr still catalyzed the formation of **2b** to a yield of 65% and chemoselectivity 6.4:1. **2c**-**2f** yields were also good (67-71%) and good chemoselectivity was achieved. For the reaction of **1f**, **2f** was the sole observed product.

We synthesized **1g** with an electron deficient *p*-NO_2 benzyl-group as well as **1h** with N-Me group to test if the N-Bn protecting

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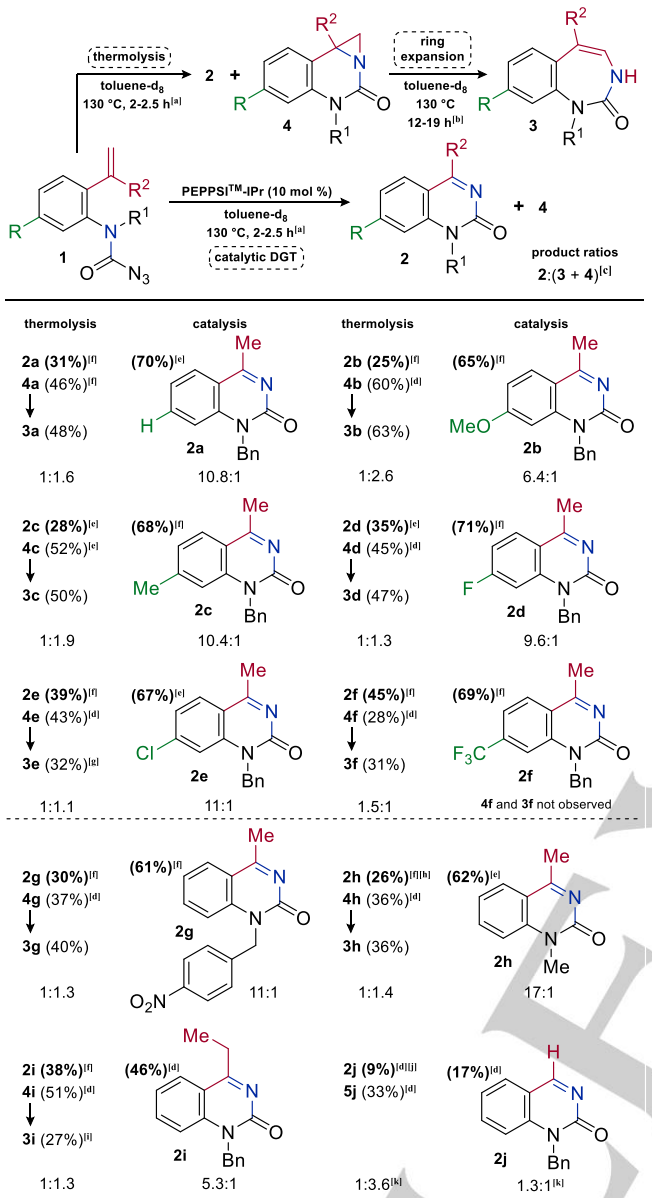

Scheme 2. Substrate Scope [a] yields assessed at both 2 h and 2.5 h, and maximum yield is reported [b] see supporting information for specific substrate reaction time [c] chemoselectivity ratios calculated with maximum yields from any timepoint [d] 2 h [e] 2.5 h [f] yield same at both timepoints [g] 9% **4e** remained [h] 14% likely **5h** obtained [i] 12% **4i** remained [j] timepoints taken at 2 h and 20 h due to slower reaction, **2j** not isolated but downfield ^{1}H NMR peak at δ = 8.54 indicative of quinazolinone product.[k] ratio given is **2j**:**5j**, **5j** being the H-shift product equivalent to **1a**

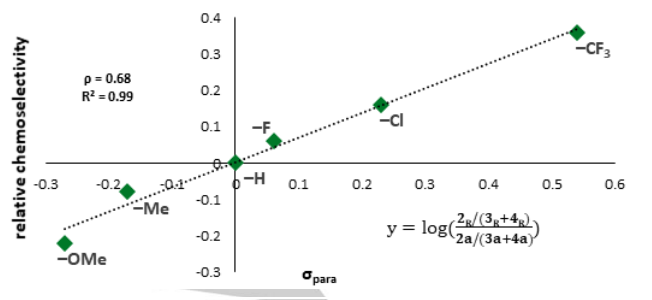

Figure 2. Chemoselectivity Hammett LFER

group has a role in catalyst activity. Both substrates behaved similarly to **1a**. PEPPSI™-IPr catalyzed the formation of **2g** and **2h**, and ring expansion products **3g** and **3h** were obtained in the uncatalyzed reaction. Next, we synthesized derivatives with alterations to the alkene; butenyl azide **1i** and styrenyl azide **1j**. Azide **1i** reacted in an analogous manner to **1a**, however the catalyzed reaction gave slightly reduced yield of **2i** (46%). Under thermolytic conditions **1j** selected significantly for the H-shift product **5j** instead of **2j** and **4j**. **2j** was speculated to have formed in only a minor quantity based on the ^{1}H NMR spectrum (see supporting information). However, PEPPSI™-IPr was still slightly active and increased the yield and chemoselectivity for DGT product **2j**.

We propose the following mechanisms to account for our kinetic data and synthetic results. Under thermolysis conditions rate-controlling (3+2) cycloaddition (**A**) leads to intermediate triazoline **I** and competing Curtius rearrangement (**B**) leads to intermediate aminoisocyanate **II** (**Scheme 3**, **a**). **I** is favored 3.9:1 over **II** based on our initial rates measurements of **1a**. Based on reported triazoline decomposition mechanisms, **I** ring opens (**C**) to the diazonium **III**, at which point the chemoselectivity divergence of interest occurs.[6a] C–C bond cleaving DGT (**D**) leads to quinazolinone **2a** with elimination of CH_2N_2, which may further decompose under the reaction conditions.[19] However, **III** favors 3-exo-tet aziridination (**E**) with expulsion of N_2 to form **4a**, which undergoes relatively slow rearrangement to benzodiazepinone **3a** via a plausible 1,2-hydride shift (**F**).[16] Since the product ratios for our Hammett LFER analysis were calculated as (**2**:(**3** + **4**)) and ρ = 0.68, it indicates that negative charge builds as **2** forms (**Scheme 3**, **b**). Therefore, the electronic influence on chemoselectivity arises from the rings' ability to stabilize or destabilize the negative charge that builds at the benzylic position, which alters the barrier of DGT. On the other hand, 3-exo-tet aziridination should be less impacted by changes to the ring electronics (**Scheme 3**, **c**). Thus, the σ_{para} LFER observed is likely a reflection of mostly the $\Delta\Delta G^{\ddagger}$ for DGT.

In the presence of PEPPSI™-IPr, we propose an interaction between either intermediate **I** or **III** and Pd alters the $\Delta\Delta G^{\ddagger}$ between the DGT path and aziridination. Since the reaction is zeroth order overall in Pd, kinetics data is unable to lend evidence as to how this process works. Presumably, rate-controlling cycloaddition produces minute concentrations of **I**, and then **I** or **III** reacts with Pd in a bimolecular process. If Pd irreversibly traps **I** or **III** then the $\Delta\Delta G^{\ddagger}$ between the two paths may result either from the barrier of aziridination increasing, the barrier of DGT decreasing, or a combination of both. If the Curtin-Hammett principle is operative, and binding between an intermediate and Pd is reversible, then the barrier for DGT from the Pd-bound intermediate may be lower relative to the noncatalyzed DGT. (**Scheme 3**, **d**). We propose this to be most plausible and triazoline **I** exchanges reversibly with 3-chloro-pyridine binding to Pd at the once terminal nitrogen of the azide to form **I•Pd** (**G**).[20] From this species a β-carbon elimination may initiate a cycloreversion process to cleave the C–C bond and eliminate **2a** from the complex (**H**)(**Scheme 3**, **e**).[21] This forms **IV** with CH_2N_2 bound to the Pd which may either exchange with the pyridine to reform PEPPSI™-IPr (**I**) or the cycle continues by exchange of CH_2N_2 with **I** (**J**).[22]

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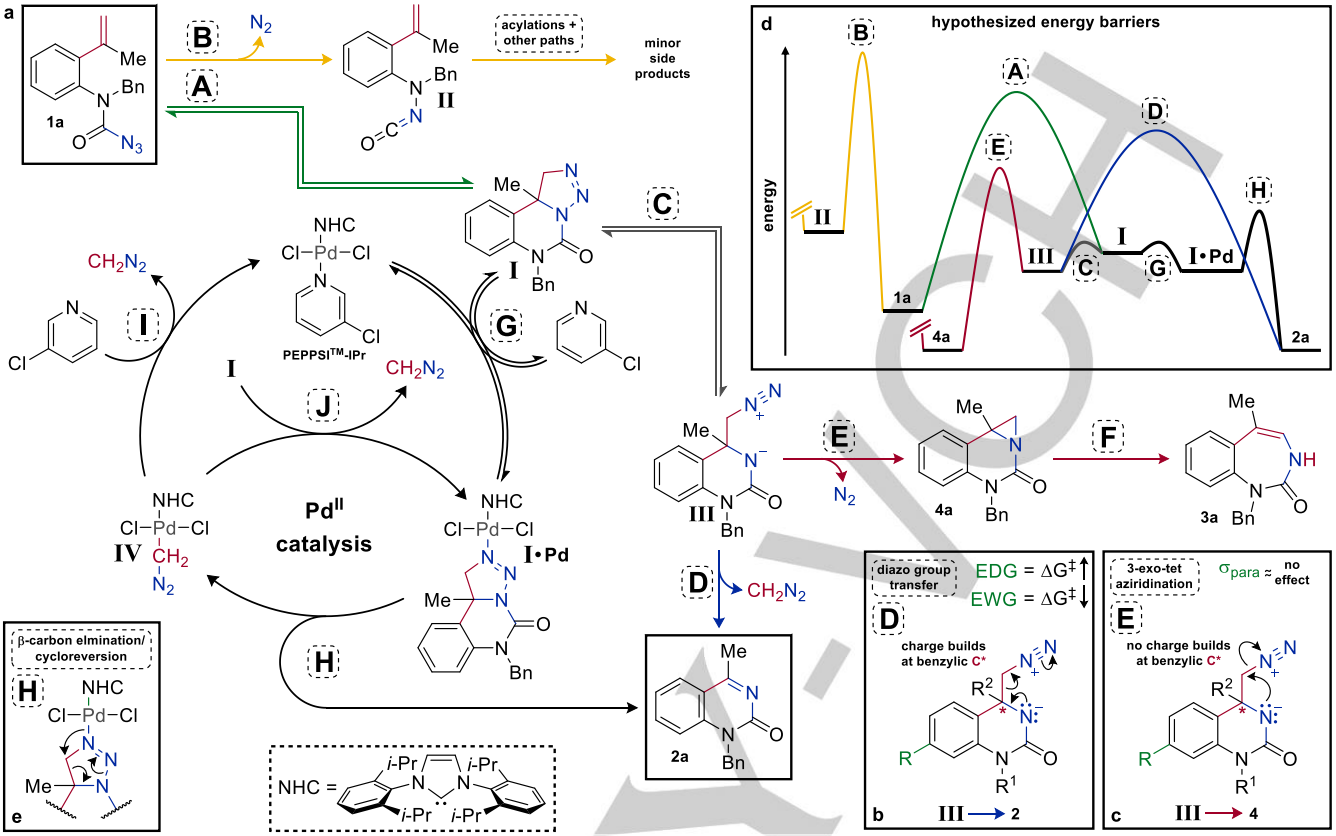

Scheme 3. Plausible PEPPSI™-IPr catalysis and thermolysis mechanisms

In summary, we have presented a Pd^{II}-catalyzed intramolecular DGT from azides to alkenes. Catalyst based chemoselectivity is achieved after the rate-controlling step, plausibly through interaction with the intermediate triazoline. This represents a new mode of metal-catalyzed chemoselective control in azide/alkene reactions. We applied the DGT reaction to synthesize medicinally relevant N-heterocyclic quinazolinones and demonstrated the competing aziridination may be a useful method to synthesize benzodiazepinones.

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Conflicts of Interest

The authors declare no conflicts of interest

Keywords: palladium • azide • cycloreversion • diazo group transfer • alkene cleavage

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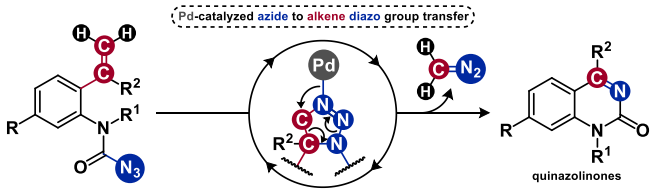

Promoting Reversion: Palladium-catalyzed intramolecular azide to alkene diazo group transfer enables the synthesis of N-heterocyclic quinazolinones. Our data support a new mode of azide/alkene metal-catalysis, a cycloreversion mechanism which grants chemoselectivity over competing aziridination.

*Grant B. Frost, Michaela K. Mittelstaedt and Christopher J. Douglas**

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Chemoselectivity for Alkene Cleavage by Palladium-Catalyzed Intramolecular Azide to Alkene Diazo Group Transfer