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Catalytic aziridination with alcoholic substrates via a chromium tetracarbene catalyst†

C. Luke Keller^a, Jesse L. Kern^{a,‡}, Bradley D. Terry^a, Sharani Roy^a, and David M. Jenkins^a

^aDepartment of Chemistry, University of Tennessee, Knoxville, Tennessee 37996, USA

Abstract

The first examples of aziridination catalysis with a chromium complex are communicated. This tetracarbene chromium complex provides novel catalytic aziridination reactions with protic substrates such as alcohols or amines on the alkene or organic azide and is the most effective catalyst at low alkene loading for aliphatic alkenes to date.

The protean reactivity of aziridines is derived from both the strain of their three-membered ring as well as the reactivity of the nitrogen atom integrated within.^{1–3} These combined properties have made aziridines invaluable for setting stereochemistry through ring opening reactions,^{4–6} and for production of larger N-heterocycles, such as 1,2,4-triazines or pyrroloindolines, via ring expansion.^{7–10} Justifiably, aziridination has been employed in the synthesis of pharmaceuticals and natural products.^{4, 11, 12}

Since aziridines can be highly effective for a variety of synthetic tasks, multiple new routes for their synthesis have been developed recently.^{13–15} Due to the wide availability of the reagents, one preferred method is the combination of alkenes and organic azides, in a C₂ + N₁ reaction.^{15, 16} To this end, Zhang, Che, Cenini, Gallo, Betley and others developed a variety of catalysts, notably porphyrins and half-porphyrins that are effective for aziridination.^{16–22}

Despite the recent improvements for this reaction methodology, there are several limitations to the C₂ + N₁ aziridination with organic azides which have prohibited the reaction's widespread application in synthetic chemistry. Typically, aziridination reactions require excess alkene relative to the organic azide.^{19, 23} The high alkene loading requirement is particularly true for aliphatic alkenes as opposed to conjugated alkenes such as styrene.^{22, 24} In the original iron catalyst pioneered by our group, high alkene loading was required to suppress formation of the metallotetrazene side-product.²⁵ More critically for medicinal chemists, functional group tolerance has been limited to non-protic functional groups such as nitros or halides.^{16, 19} Both of these limitations must be overcome if high value-added targets are to be synthesized efficiently directly from organic azides and alkenes.

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‡The current address for J. L. Kern is the Department of Chemistry, Randolph College, Lynchburg, VA 24503, USA.

In this communication, we present the results for aziridination catalysis with a tetracarbene chromium(III) complex.²⁶ This chromium complex is the first C₂ + N₁ aziridination catalyst on any group six metal. Unlike our previous iron systems,²⁴ the chromium complex is effective for aziridination at low alkene loadings. Furthermore, this catalyst is modestly effective at aziridination with protic functional groups on the alkene or azide, which has not been observed with any previous aziridination catalysis using organic azides. Finally, we present some preliminary observations on why the chromium catalyst is effective at low alkene loading as compared to the original iron catalyst and other similar chromium systems.

Since the success of our initial iron tetracarbene catalyst at aziridination²⁴ and our development of a methodology to prepare a wide variety of tetracarbene complexes,²⁶ we examined each additional complex for catalytic aziridination. While most were unreactive toward organic azides, the octahedral chromium complex [(^{Me,Et}TC^{Ph})Cr(Cl)₂](PF₆) (**1**) proved effective at aziridination with aryl azides in a similar manner to the previously reported [(^{Me,Et}TC^{Ph})Fe(NCCH₃)₂](PF₆)₂ (**2**). A general aziridination reaction of aryl azides and alkenes with these catalysts is shown in Scheme 1.

Optimizing the test conditions with **1** found that this catalyst was effective at low alkene loading. A test reaction of 1-decene and *p*-tolyl azide in a 1:1 ratio plus **1** at 2% catalyst loading in acetonitrile at 85 °C gave an isolated yield of 26% for 2-octyl-1-(*p*-tolyl)aziridine, **3** (Table 1, Entry 1). A modest increase in the alkene loading to a 3:1 ratio boosted the yield of **3** to 61% (Entry 2). Further increases in alkene loading only had trivial increases in the yield (Entry 3).²⁴ A pair of control reactions without **1** present produced **3** in only 4.7% and 12.3% yields for 1:1 and 3:1 alkene to azide ratios, respectively (Entries 4 and 5). Notably, the same reaction with **2** as catalyst was ineffective (Entry 6).

Test conditions for reactions with **1** also explored the effect of solvent on the reaction (ESI) under the same conditions as shown in Table 1, Entry 2. Non-polar solvents, such as toluene, showed no catalytic activity. Polar solvents including DMF, DMSO, and pyridine gave yields for the test reaction of 46%, 13%, and 31%, respectively, which were all lower than the previously described reaction in acetonitrile.

Initial investigations on catalytic aziridination focused on examples with either no functional groups or aprotic functional groups (ESI, Table S1). 9-(*p*-tolyl)-9-azabicyclo[6.1.0]nonane, **4**, was prepared in 52% yield from **1**, tolyl azide, and only three equivalents of cyclooctene, while the original iron catalyst, **2**, required neat cyclooctene for the same reaction.²⁴ In a similar manner, 1-(4-methoxyphenyl)-2-octylaziridine, **5**, 4-(2-octylaziridin-1-yl)benzaldehyde, **6**, and 1-(4-chlorophenyl)-2-octylaziridine, **7**, could be prepared in modest yields at low alkene loading (56%, 40%, and 35%, respectively). Finally, as a test with a functionalized alkene, we tested 10-undecenoate with *p*-tolyl azide and **1** to yield ethyl 9-(1-(*p*-tolyl)aziridin-2-yl)nonanoate, **8**, albeit in low isolated yield of 23%.

While catalysis reactions with aprotic organic azides and alkenes have been an intense area of research in the last decade,^{16, 19, 20} no fully characterized aziridines containing protic functional groups have been reported via C₂ + N₁ catalysis of an alkene and organic azide.²⁷

Protic functional groups are commonly found in natural products that contain aziridines.²⁸ The chromium catalyst **1** was modestly effective for several of these reactions (Table 2). Replacing 1-decene with 9-decenol led to the formation of 8-(1-(*p*-tolyl)aziridin-2-yl)octanol, **9**, in 32% isolated yield. A similar reaction with **2** as the catalyst yielded no aziridine which is consistent with our previous results that show that our iron catalysts are not effective with protic functional groups.

Moving to a shorter chain alcohol led to an unexpected product. The reaction with 4-pentenol, *p*-tolyl azide and **1** did not yield the expected aziridine, but in fact 4-methyl-N-((tetrahydrofuran-2-yl)methyl)aniline, **10**, which has been previously prepared by Buchwald via a coupling reaction of *p*-tolylboronic acid and *S*(+)-tetrahydrofurylmethyl amine.²⁹ Compound **10** could be formed through from an intramolecular ring opening nucleophilic attack of the alcohol on the expected aziridine followed by a proton shift with **1** acting as a catalyst. Several early metal catalysts have been designed for this class of reaction including stereoselective examples by Kobayashi.³⁰ Alternatively, a carboradical intermediate could be formed during formation of the aziridine which would be attacked by the alcohol. Placing alcohols off an aryl ring gave similar products. An alcohol in the *para* position of the organic azide lead to aziridine formation (**11**), while an alcohol in the *ortho* position again led to a ring opening and rearrangement (**12**) in a manner analogous to **10**.

Additional tests expanded the scope beyond placing an alcohol on the alkene (Table 2). Alcohols on the organic azide were successful as well. A catalytic reaction with 3-azidophenol and 1-decene and **1** gave the expected aziridine, 3-(2-octylaziridin-1-yl)phenol, **13**, in 35% isolated yield. Notably, a reaction with a secondary amine was also successful. N-allylaniline was combined with *p*-tolyl azide and **1**, to yield N-((1-(*p*-tolyl)aziridin-2-yl)methyl)aniline, **14**, in 30% yield. The only protic functional group tested that was completely ineffective was carboxylic acids. A reaction with 9-decenoic acid under the standard catalytic conditions yielded no aziridine.

Since catalytic aziridination often yields a mixture of products, particularly amination products, we decided to quantitate the balance of products for selected reactions.¹⁷ We tested the formation of **9** and **13** under the same catalytic conditions in CD₃CN and integrated the products versus an internal standard of CH₂Br₂ (Table 3). In the case of **9**, we noted a 50% conversion to the desired azide, which shows that the low yield of **9** is primarily due to the challenging separation. In addition to the aziridine, both unreacted azide and alkene were present in 30% and 250% yield, respectively. In addition, some tolyl azide had also been reduced to the respective amine (18% yield); amine side products in aziridination have been previously reported.¹⁷ Notably, neither vinylic or allylic amination products were detected in the NMR. A similar reaction to form **13** showed the same products in qualitatively similar ratios.

The relative effectiveness of **1** at low alkene loading as compared to **2** led us to consider their mechanistic differences. First, compound **1**, like **2**, is a saturated octahedral complex. While **2** exchanges its solvent ligands rapidly,²⁴ **1** would need to lose a chloride to have an open site (Scheme 2). We believe that the different rates of catalysis for **1** as a function of solvent are related to this effect (ESI). Non-polar solvents are ineffective for catalysis, while

acetonitrile is the most favorable. Once a site is open, an organic azide could react to form a metal imide. DFT calculations (see ESI) show that this reaction is highly favorable by $\Delta G = -57.4$ kcal/mol to form a species with one chloride removed (Scheme 2). At this point, the chromium imide intermediate could either react with a second azide to form a metallotetrazene or an alkene to form an aziridine. DFT calculations show that the formation of aziridine is more favorable ($\Delta G = -43.9$ kcal/mol) than the formation of metallotetrazene ($\Delta G = -33.8$ kcal/mol). This theoretical result is consistent with our observation that **1** is effective at low alkene loading unlike **2**.

The formation of metallotetrazene appears to be disfavored solely by the *trans* chloride ligand on **1**. This supposition is supported by DFT calculations which show that the purported imide intermediate is favorable both with and without a *trans* chloride, but the presence of the *trans* chloride destabilizes a metallotetrazene relative to the formation of aziridine (Figure S21 and S22, ESI). If the *trans* chloride is removed, the relative free energy of the tetrazene drops to $\Delta G = -72.9$ kcal/mol (versus $\Delta G = -33.8$ kcal/mol with chloride) which would make metallotetrazene formation highly favorable. These theoretical results were tested with a series of reactions with halide abstracting reagents. Addition of two equivalents of halide abstraction reagent, in this case a silver ion, during a catalytic reaction completely stops aziridination. A single equivalent of halide abstractor (either Tl or Ag) reduced the yield of aziridine (23% and 18%, respectively). These low yields suggest that it may be easier to remove the second equivalent of chloride during the catalytic cycle, perhaps upon formation of the chromium imide species that would have a strong *trans* effect.

A key question is why catalyst **1** is effective at aziridination while other chromium systems have not reported this reaction. Similar catalytic oxygen atom transfer oxidations with chromium are known, but rare. A few epoxidations with Cr(III) systems are known (and proceed through Cr(V) oxos),^{31, 32} and the yields are modest (less than 50%). Turning to imide analogs, Cr(V) imides have been reacted with phosphines to give the phosphiimide,³³ but in some cases Cr(V) imides have been isolated for which no reactivity was reported. The most prominent studies for Cr(V) have featured auxiliary ligands such as salen, porphyrin, or corroles.^{34, 35} Notably, our recent research with a similar tetracarbene Cr(IV) imide complex demonstrates non-catalytic imide transfer.³⁶ We suspect that **1** is more reactive both due to the stronger donor NHCs and the key *trans* chloride ligand. The former explains why relatively weak oxidants like aryl azides are reactive as opposed to only stronger oxidants that have been previously employed (like PhIO). The latter, the lack of a ligand *trans* to the imide, is a key feature which promotes reactivity with an alkene as shown in our DFT calculations. None of the previous examples of chromium group transfer catalysis feature a ligand that is *trans* to the purported imide.

In conclusion, we have demonstrated a novel chromium catalyst for $C_2 + N_1$ aziridination, the first on this metal. This catalyst is effective at low alkene loading, unlike our initial iron catalysts, and is the most effective catalyst for aliphatic alkenes at low loading to date. More impressively, this chromium catalyst is the first example that is effective with protic functional groups, such as alcohols or amines, albeit in modest isolated yields. Including these functional groups on aziridines is critical for developing improved synthetic methods in medicinal chemistry. These insights are critical for designing the next generation of $C_2 +$

N₁ aziridination catalysts and suggest that additional chromium complexes should be tested as catalysts for aziridination.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Example catalytic aziridination reaction with Cr (**1**) or Fe (**2**) catalysts.

Scheme 2.

Proposed catalytic cycle for **1**. Calculated free energies (ΔG) for the species are shown in blue in units of kcal/mol.

Table 1

Testing catalytic conditions for various alkene loadings.

Entry ^a	Catalyst ^b	Azide/Alkene ratio	Catalyst Loading	Isolated Yield of 3
1	1	1/1	2%	26.3
2	1	3/1	2%	61.1
3	1	10/1	2%	67.2
4	1	1/1	0%	4.7
5	1	3/1	0%	12.3
6	2	3/1	2%	9.7

^a 4 mL of CH₃CN as solvent at 85°C for 3 days. 1-decene (variable) and *p*-tolyl azide (~100 mg) were used in each test reaction as shown in Scheme 1.

^b 0.01-0.02 mmol of **1** or **2** was used for each reaction.

Table 2Catalytic reaction with **1** and protic functionalized alkenes and organic azides.

Entry ^a	Alkene	Azide	Product	Isolated Yield
1				31.8
2				41.3
3				26.1
4				39.1
5				35.0
6				30.1

^a 4 mL of CH₃CN as solvent at 85°C for 3 days. **1** employed as catalyst at 2% loading with a 3/1 alkene to azide ratio.

Table 3

Quantification of product distribution at conclusion of reactions by NMR integration.

Entry ^a	Azididine	Conversion/Isolated Yield	Remaining Azide/Alkene ^b	Amine
1	9	50/31.8	30/250	18
2	13	44/35.0	28/231	28

^a 4 mL of CD₃CN as solvent at 85°C for 3 days. **1** employed as catalyst at 2% loading with a 3/1 alkene to azide ratio. CH₂Br₂ was employed as an internal standard.

^b Three equivalents of alkene were employed so multiple equivalents remained.