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Aziridination of Aliphatic Alkenes Catalyzed by *N*-Heterocyclic Carbene Copper Complexes

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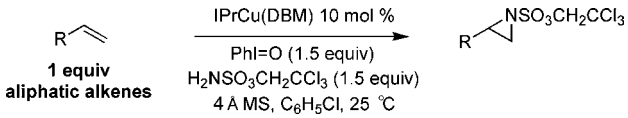
ABSTRACT



A copper-catalyzed aziridination of aliphatic alkenes promoted by *N*-heterocyclic carbene ligands is described. The readily available catalyst IPrCu(DBM) can catalyze aziridination of a variety of aliphatic alkenes using alkenes as the limiting reagents.

Aziridines are versatile synthetic intermediates and are also present in many biologically active compounds.[1] Among the methods to access aziridines, nitrene addition to alkenes constitutes one of the most straightforward synthetic strategies.[2] This type of reaction may proceed through a copper−nitrene intermediate derived from a copper catalyst and *N*-(*p*-tosyliminophenyliodinane) (TsN═IPh).[3] In many aziridination methodologies, efficient trapping of a nitrene by an alkene can be difficult and may require the use of a large excess of alkene (such as 5−10 equiv). This is not practical when the starting material is a valuable synthetic precursor. Moreover, high yields for aziridinations are usually limited to substrates derived from styrene whereas simple aliphatic alkenes often exhibit diminished reactivity or competing side reactions resulting from C−H insertion. Even with these shortcomings, there are notable applications of alkene aziridination in organic synthesis,[1,4] but improvements could benefit researchers.

Recent studies on metal−nitrene catalysts have demonstrated that an iminophenyliodinane may be generated in situ in the presence of an oxidant, such as iodosobenzene or iodobenzene diacetate, and a sulfonamide.[5] In the presence of a metal (such as copper,[6] rhodium,[7] ruthenium,[8] manganese,[9] silver,[10] gold,[11] iron,[12] and cobalt[13]), metal−nitrene catalysts can be generated. One of the best aziridination catalysts developed so far is the Rh-based system reported by Du Bois and co-workers that has excellent reactivity with numerous types of substrates (including aliphatic alkenes),

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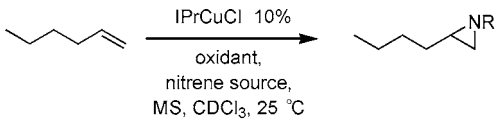
utilizes only a single equivalent of substrate, and is stereospecific.[7c,i] The only minor drawback to this system is the substantial amount of competitive C−H insertion observed with cyclohexene and cyclopentene which limited its use for our research purposes.[14] Yudin and co-workers have developed an elegant aziridination method that relies on electrochemical oxidation of *N*-aminophthalimide. This method has the broadest substrate scope but also requires specialized apparatus.[2e,15] Therefore, we pursued the development of a simple aziridination catalyst specifically for cyclic and aliphatic alkenes that are relevant to our research program.[14]

Whereas most aziridination catalysts rely on nitrogen ligands, we felt that *N*-heterocyclic carbenes (NHC)[16] could potentially be better ligands to promote the reaction by stabilizing reactive intermediates in the catalytic cycle.[17] In addition, carbene metal catalysts are robust, highly tolerant to oxidizing conditions, and NHC copper carbene complexes have been shown to catalyze cyclopropanation over C−H insertion.[18] To the best of our knowledge, there are only two examples of aziridination using NHC metal complexes. Trost and Dong reported successful aziridination of an aliphatic alkene with 50% IPrCuCl as a catalyst and 5 equiv of TsN═IPh in the total synthesis of Agelastatin A.[19a] Recently, Fleming and co-workers employed the same catalyst to promote an intramolecular aziridination of unsaturated *N*-tosyloxy carbamates.[19b] In this manuscript, we report a systematic investigation of aziridination using copper catalysts bearing NHC ligands under conditions where the nitrene is generated in situ. Furthermore, we optimized conditions so that the substrates are not used in excess, and we specifically focused on using aliphatic alkenes as substrates.

In developing our methodology, we selected copper as the metal because copper nitrene complexes usually react with alkenes via an aziridination pathway over competing allylic amidation.[3] Using IPrCuCl (a commercially available NHC copper complex) as the catalyst and 1-hexene as the substrate, we found that reactions were highly dependent upon oxidants and nitrene sources. In our hands, PhI═NTs produced aziridine in low conversion (Table 1, entry 1) and iodobenzene diacetate gave no product under various conditions (entries 2−4). Iodosobenzene proved to be the best oxidant. Next, the role of the sulfonamide was investigated. As shown

Table 1. Aziridination of 1-Hexene Catalyzed by IPrCuCl[a]



entry	oxidant	nitrene source	% conversion[b]
1	PhI═NTs		35
2	$PhI(OAc)_2$	$TsNH_2$	<2
3	$PhI(OAc)_2 + MgO$	$TsNH_2$	<2
4	$PhI(OAc)_2 + Al_2O_3$	$TsNH_2$	<2
5	PhIO	$TsNH_2$	32
6	PhIO	$NsNH_2$	14
7	PhIO	$MpsNH_2$	27
8	**PhIO**	**$H_2NSO_3CH_2CCl_3$**	**66**
9	PhIO	$H_2NSO_3CH_2CCl_3$	<2[c]

[a] All reactions were performed with 0.1 mmol 1-hexene, 0.01 mmol catalyst, 0.11 mmol oxidant and nitrene source, 80 mg 4 Å molecular sieves (MS) in 0.5 mL $CDCl_3$ at room temperature (25 °C) for 20 h. [b] Determined by ^1H NMR. [c] Reaction without MS.

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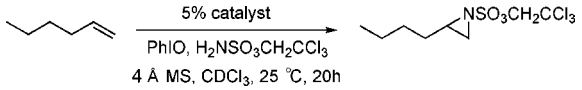
in Table 1, toluenesulfonamide ($TsNH_2$), *p*-nitrobenzenesulfonamide ($NsNH_2$),[6d] and 5-methylpyridine-2-sulfonamide ($MpsNH_2$)[6p] were moderately efficient, but the best result was achieved with the trichloroethylsulfamate ester ($H_2NSO_3CH_2CCl_3$) that was pioneered by Du Bois and co-workers for aziridination with their Rh-based catalyst.[7c,i] This sulfonamide group may be removed using Zn(Cu) in AcOH/MeOH.[7c] In contrast to the procedure reported by Dauban and Dudd,[5a] 4 Å molecular sieves (MS) were essential for this transformation (compare entries 8 and 9). In addition, other dehydrating agents (trimethyl orthoformate and $MgSO_4$) were not effective. To determine whether the NHC ligand was important for the reaction, the same conditions of entry 8 were performed using CuCl and $CuCl_2$ instead of IPrCuCl. In these cases, no aziridine product was formed.

Next, we continued to optimize the conditions of entry 8 from Table 1. Reactions using catalysts derived from more sterically demanding ligands (IPr, IAd) proceeded with higher conversions than ones with less hindered ligands (IMes, ICy) (Table 2, compare entries 1, 2, 4, 5, and 6). Imidazole and

Table 2. Aziridination of 1-Hexene Catalyzed by Various Copper-carbene Complexes[a]

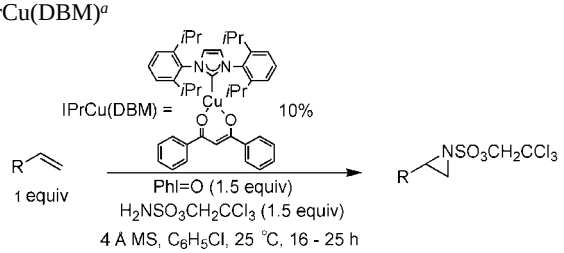


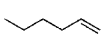
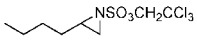
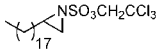
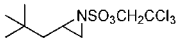
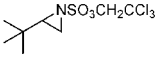
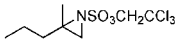
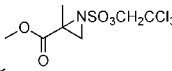
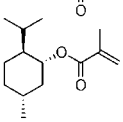
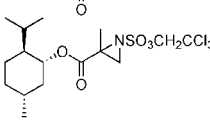
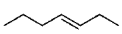
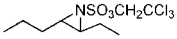
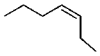
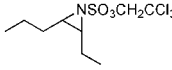
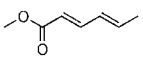
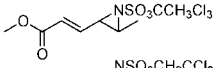
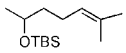
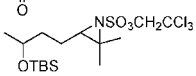
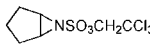
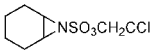
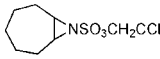
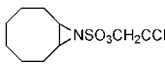
entry	catalyst	% conversion[b]	entry	catalyst	% conversion[b]
1	IMesCuCl	22	7	IPrCuOTf	<2
2	IPrCuCl	29	8	IPrCuCl/ NaBAr4	11
3	SIPrCuCl	34	9	IPrCuCl/ $AgSbF_6$	<2
4	IAdCuCl	39	10	$IPrCu(OAc)_2$	<2
5	IBuCuCl	22	11	IPrCu(acac)	43
6	ICyCuCl	17	12	IPrCu(DMB)	62

[a] All reactions were performed with 0.1 mmol 1-hexene, 0.005 mmol catalyst, 0.11 mmol oxidant and nitrene source, 80 mg 4 Å molecular sieves (MS) in 0.5 mL $CDCl_3$ at room temperature (25 °C) for 20 h. [b] Determined by ^1H NMR.

dihydroimidazole derivatives showed similar reactivity (entries 2 and 3). The counterion of these complexes has a significant effect: for instance, replacing chloride with a weakly coordinating ion decreases reactivity (entries 7−9). Interestingly, the Cu(II) carbene complex $IPrCu(OAc)_2$ was unreactive. Fortunately, 1,3-diketone ligands afforded the highest yields. For instance, when dibenzoylmethane (DBM)

Table 3. Aziridination of Olefins Catalyzed by 10% IPrCu(DBM)[a]



entry	alkene	aziridine	yield[b]
1			75
2			61
3			76
4			51
5			61
6			82
7			63[c]
8			35[d]
9			56[e]
10			50[f]
11			86
12			57[g]
13			43[h]
14			71
15			88

[a] All reactions were performed with 0.5 mmol alkene, 0.05 mmol IPrCu(DBM), 0.75 mmol, PhI═O and 0.75 mmol $H_2NSO_3CH_2CCl_3$, 600 mg 4 Å powdered molecular sieves (MS) in 1.25 mL C_6H_5Cl at room temperature for 16−25 h. [b] Isolated yield. [c] Diastereomer ratio 1:1. [d] Combined yield, *trans*:*cis* = 8:1. [e] Combined yield, *trans*:*cis* = 1:2.6. [f] *Trans* only. [g] Seven percent allylic amination product. [h] Ten percent allylic amination product.

is the counterion instead of chloride, the conversion increased from 29 (entry 2) to 62% (entry 12). Therefore, the best copper complex for this reaction is IPrCu(DBM), a complex previously developed by Nolan and co-workers to catalyze a reductive aldol reaction.[20]

Once the best copper complex, oxidant, sulfonamide, and the proper amount of MS were identified, additional param-

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eters were optimized. A brief comparison of solvents demonstrated that benzene and chlorobenzene were better than CH_2Cl_2, toluene, or CH_3CN. Ultimately, the ideal conditions for aziridination of 1-hexene were: 10% IPrCu(DBM),[20] 1.5 equiv of PhIO and trichloroethylsulfamate ester in chlorobenzene at room temperature (25 °C) for 16−25 h under an inert atmosphere of nitrogen. Under these conditions, the product from aziridination of 1-hexene was isolated in 75% yield (Table 3, entry 1). Although portionwise addition of oxidant is necessary in some aziridination reactions,[21] a benefit of our method is that all reagents are combined simultaneously in one flask at room temperature.

Application of the optimized conditions to a variety of aliphatic alkenes yielded the corresponding aziridines in moderate to high yields. Terminal olefins are generally suitable substrates (Table 3, entries 1−7). The reaction is sensitive to steric hindrance, as seen in the lower yields for entries 4, 8, and 9. For 1,2-disubstituted alkenes, there was significant loss of stereochemistry from the starting material. In the case of *trans*-2-heptene (entry 8), the azirdine product was obtained with a *trans*:*cis* ratio of 8:1. For *cis*-2-heptene, the products had a *trans*:*cis* ratio of 1:3.

A loss in stereospecificity has been observed in previous studies of metal-catalyzed aziridination,[3a,6p,6t,8a,19b] and indicates that a two-step radical pathway is a possible mechanism.[2a,22]

Fortunately, electron deficient alkenes perform very well as substrates. For instance, aziridination of methyl methacrylate afforded the product in high yield (entry 6). The corresponding *O*-menthyl ester was also aziridinated, but there was no diastereoselectivity (entry 7). However, published procedures could be used to separate these diastereomers by fractional crystallization, and thus provides a access to enantiomerically pure aziridine derivatives.[23] Interestingly, the conjugated diene ester (2*E*, 2*E*)-methyl hexa-2,4-dienoate was aziridinated with high regio- and stereoselectivity (entry 10) to afford a vinyl aziridine that could be a versatile synthetic intermediate.[1c] Currently, unprotected alcohols are not compatible in this reaction. However, aziridination of TBS-protected 6-methyl-5-hepten-2-ol proceeded very well (entry 11). Aziridination of cyclic substrates (entries 12−15) worked best with cycloheptene and cyclooctene. Cyclohexene and cyclopetene are known to be challenging substrates for aziridination reactions due to the formation of products derived from allylic amidation. Using our reaction conditions, moderate yields of aziridine were obtained along with minor amounts of allylic amines (5−10%).

In summary, we have developed a practical aziridination method catalyzed by the copper complex IPrCu(DBM).[20] Under the optimized conditions, a wide variety of aliphatic alkenes were converted to aziridines in moderate to high yields using the substrates as the limiting reagents. Furthermore, the ease with which the catalyst can be prepared along with the simplicity of the reaction protocol make this methodology practical for use with a variety of substrates.

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Note Added after ASAP Publication. In the version published March 12, 2008 the 4 was missing from the MS below the arrow in the abstract and Tables 2 and 3; this was corrected in the version published March 13, 2008.

Supporting Information Available: ^1H and ^{13}C NMR data for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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