

Simple, Tunable Aziridination Catalysts Based on Poly(pyrazolyl)borate–Copper Complexes

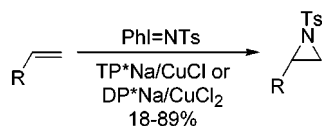
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ABSTRACT



The in situ generation of a copper–poly(pyrazolyl)borate complex from copper chloride and a sodium poly(pyrazolyl)borate salt results in a catalyst that is effective for the aziridination of olefins. A significant influence of the combination of the starting copper oxidation state and the hapticity of the poly(pyrazolyl)borate ligand on the efficiency of the reaction has been observed.

Strained rings continue to be the subject of considerable interest and utility in organic synthesis.¹ While cyclopropanes and epoxides have garnered the most attention, the nitrogen-containing members of this series, aziridines, serve an important role as the reactive core of several biologically interesting natural products (such as mitomycin and azinomycin) and as versatile synthetic intermediates in route to simple amines, amino alcohols, and diamines.² Their “second-class” status in large part stems from the lack of a general, simple, and efficient means of preparing aziridines. Perhaps the most straightforward synthetic strategy is the cycloaddition of an olefin with a nitrogen source. Not surprisingly, this parallels the most common methods of preparing epoxides (using peracids or peroxides) and cyclopropanes (using carbenes or carbenoids). Unlike the carbon and oxygen systems, though, this [2 + 1] route to aziridines remains problematic. The obvious nitrogen source for these reactions, a nitrene, is extremely reactive and will undergo a variety of reactions beyond simple aziridination.³ Although similar

difficulties with the use of carbenes have been largely resolved by the use of metal catalysts, the same approach toward control of nitrene reactivity has not progressed to a synthetically advanced state.

A number of catalyst systems (mostly based on copper) have been reported,⁴ but they all have significant limitations. First, with only one exception,⁵ all catalytic systems require at least 5 mol % of the catalyst to achieve optimal yields. Second, reaction yields are good for aryl-substituted olefins (such as styrene) but are unacceptably low for simple aliphatic olefins such as cyclooctene. The reasons for this limitation are unclear. Indeed, detailed experimental mechanistic information regarding metal-catalyzed aziridination reactions is sparse.⁶ The combination of poor substrate scope

(3) For a review of nitrene chemistry, see: Gilchrist, T. E.; Rees, C. W. *Carbenes, nitrenes, and arynes*; Nelson Press: London, 1969.

(4) For examples of catalysts used in aziridinations, see: (Copper) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742. Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326. Vyas, R.; Chanda, B. M.; Bedekar, A. V. *Tetrahedron Lett.* **1998**, *39*, 4715. Ando, T.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron Lett.* **1998**, *39*, 309. (Rhodium) Albone, D. P.; Aujla, P. S.; Taylor, P. C. *J. Org. Chem.* **1998**, *63*, 9569. Mueller, P.; Baud, C.; Jacquier, Y. *Can. J. Chem.* **1998**, *76*, 738. (Iron and Manganese) Mansuy, D.; Mahy, J.-P.; Dureault, A.; Bedi, G.; Battieoni, P. *J. Chem. Soc., Chem. Commun.* **1994**, 1161. Simanot, J.-P.; Pecaut, J.; Scheidt, W. R.; Marchon, J.-C. *Chem. Commun.* **1999**, 989.

(5) Halfen, J. A.; Hallman, J. K.; Schultz, J. A.; Emerson, J. P. *Organometallics* **1999**, *18*, 5435.

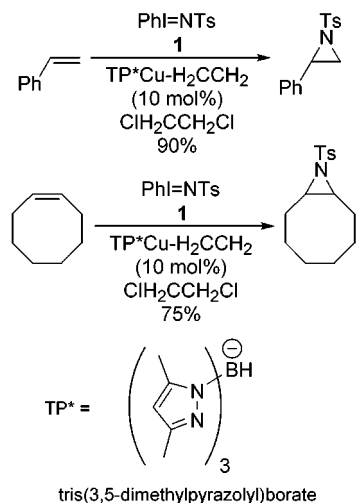
(1) For a recent review, see: *Small Ring Compounds in Organic Synthesis VI*; De Meijere, A., Ed.; Topics in Current Chemistry; Springer-Verlag: Berlin, 2000; Vol. 210.

(2) Padwa, A.; Woolhouse, A. D. In *Comprehensive Heterocyclic Chemistry: The Structure, Reactions, Synthesis, and Uses of Heterocyclic Compounds*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 7, p 47. Kemp, J. E. G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 7, p 469.

and limited mechanistic understanding continues to hinder the development of a simple aziridination reaction.

A major step toward solving this problem was reported several years ago by Brookhart. He reported the use of a tri(pyrazolyl)borate–copper(I) complex with ethylene as a catalyst for both cyclopropanation and aziridination reactions.⁷ As shown in Scheme 1, this catalyst was effective in

Scheme 1. Aziridinations Using a Tri(pyrazolyl)borate–Copper Catalyst⁷



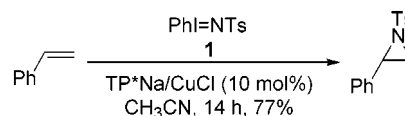
the aziridination of styrene (90%). More notably, aliphatic olefins such as cyclooctene also afforded good results (76%).

Brookhart's catalyst is a very promising aziridination catalyst, but it still retains one significant limitation: it must be prepared and used in a drybox or with good Schlenk techniques. This oxidative instability is typical of copper(I) complexes in general and not simply the tris(3,5-dimethylpyrazolyl)borate (TP*) complex. Indeed, the parent TP* ligand itself is remarkably stable.⁸ Thus, a potential solution to this oxidative instability is to generate the catalyst in situ from the stable precursors sodium TP* and copper(I) chloride. This obviates the typical concerns associated with the handling and use of copper(I) complexes.

Initial attempts to generate the Brookhart catalyst in situ in dichloroethane from copper(I) chloride and sodium tris(3,5-dimethylpyrazolyl)borate afforded only 5% of the desired aziridination product. This result is likely due to the insolubility of copper(I) chloride and the very limited solubility of sodium TP* in dichloroethane. While a variety of more polar solvents could solve the solubility problem,

acetonitrile is generally an excellent solvent for simple aziridinations due to the high affinity of copper for acetonitrile and the formation of stable copper–acetonitrile complexes. In the event, treatment of a solution of styrene in acetonitrile with 10 mol % of copper(I) chloride and 10 mol % of sodium tris(3,5-dimethylpyrazolyl)borate under argon resulted in the rapid formation of a homogeneous solution. Subsequent addition of iodane **1** followed by a standard aqueous workup and chromatography afforded the desired aziridine in 77% isolated yield (Scheme 2).⁹

Scheme 2 In Situ Catalyst Generation



Given the success of the in situ generation of TP*Cu, attempts were made to further optimize the catalyst system. First, the influence of the starting oxidation state of copper was explored. The vast majority of previously reported catalyst systems used in aziridinations note little difference in the activity of the copper(I) and copper(II) catalysts. This is not the case with the TP*-derived catalyst systems. As shown in Table 1 (entries 1 and 2), attempts to use copper-

Table 1. Influence of Hapticity and Oxidation State on Reactivity^a

Catalyst	Yield
TP*Na/CuCl	72-77%
TP*Na/CuCl ₂	28-32%
DP*Na/CuCl	56-60%
DP*Na/CuCl ₂	84-89%

^a All yields are the range obtained from at least three separate reactions.

(II) chloride in place of copper(I) chloride afforded much lower yields.

The second feature that can be readily modified using the poly(pyrazolyl)borate catalyst systems is the hapticity of the poly(pyrazolyl)borate ligand. To date, virtually all ligand-modified catalyst systems reported for aziridination reactions

(6) For selected mechanistic studies, see: Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742. Diaz-Requejo, M. M.; Perez, P. J.; Brookhart, M.; Templeton, J. L. *Organometallics* **1997**, *16*, 4399. Li, Z.; Quan, R. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5889. Mueller, P.; Baud, C.; Jacquier, Y. *Can. J. Chem.* **1998**, *76*, 738. Brandt, P.; Soedergren, M. J.; Andersson, P. G.; Norrby, P.-O. *J. Am. Chem. Soc.* **2000**, *122*, 8013.

(7) Perez, P. J.; Brookhart, M.; Templeton, J. L. *Organometallics* **1993**, *12*, 261.

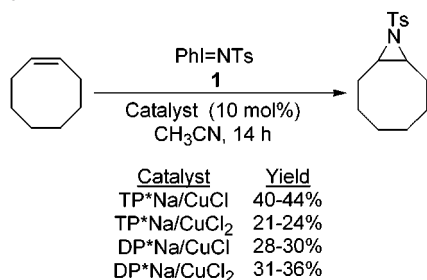
(8) For a review of poly(pyrazolyl)borates in general, see: Trofimenko, S. *Chem. Rev.* **1993**, *93*, 943.

(9) **Representative Procedure:** To a dry vial under argon was added 2.7 mL of distilled acetonitrile. After argon was bubbled through this solution for 15 min, 8.6 mg (0.027 mmol) of sodium tris(3,5-dimethylpyrazolyl)borate and 2.7 mg (0.027 mmol) of copper(I) chloride were added. The solution was stirred for 5 min, whereupon 0.15 mL (1.34 mmol) of styrene and 100 mg (0.268 mmol) of the iodane were added. The reaction was stirred under argon for 14 h and then quenched by the addition of 3 mL of water. This mixture was extracted with ethyl acetate (3 × 5 mL), dried with magnesium sulfate, and concentrated in vacuo. The crude residue was purified by flash column chromatography (7% ethyl acetate in hexanes as eluent) to afford 56.5 mg (77%) of the aziridine product as a white solid.

have been bidentate, while the tri(pyrazolyl)borate ligands are presumably tridentate. In an effort to determine the potential influence of hapticity on the aziridination reaction, the requisite bis(3,5-dimethylpyrazolyl)borate (DP*) sodium salt was prepared using the literature procedure.¹⁰ Interestingly, this system displayed the opposite oxidation state selectivity to that observed with the TP* series (Table 1, entries 3 and 4). Thus, copper(II) chloride in conjunction with sodium DP* afforded the highest isolated yields of any of the systems explored in this study.

This same series of catalyst systems were then utilized in the aziridination of cyclooctene in an effort to determine whether a similar trend would be observed with less reactive olefins (Table 2). Unlike the results obtained with styrene

Table 2. Hapticity and Oxidation State Studies on Cyclooctene^a



^a All yields are the range obtained from at least three separate reactions.

as the olefin, the use of DP*CuCl did not result in an increase in yield compared to the TP*Cu catalyst system. Indeed, the differences between the four catalyst combinations were much less pronounced for the aziridination of cyclooctene.

In exploring the scope and limitations of this in situ catalyst-generation procedure, several important trends were noted.¹¹ Not surprisingly, aromatic substituted olefins afforded good to excellent yields of the desired aziridine products (Table 3). The one exception was *trans*- β -methylstyrene, which afforded only a 27% yield of the desired aziridine. The yield of this reaction could be significantly improved (46%) by employing DP*CuCl as the catalyst. A similar effect was not observed with *cis* olefins. Thus, neither cyclooctene (Table 2) nor dihydronaphthalene (entry 4, Table 3) afforded enhanced yields. Instead the yields decreased slightly. In the case of terminal or 1,1-disubstituted olefins,

(10) Trofimenko, S. *J. Am. Chem. Soc.* **1967**, *89*, 3170.

(11) All compounds displayed spectral properties indistinguishable from those reported in the literature.

Table 3. Aziridinations Using in Situ Generated TP*Cu^a

entry	olefin	product	yield ^b
1			84% (77%) ^c
2			27% (46%) ^c
3			88%
4			56% (46%) ^c
5			18% (17%) ^c

^a The reactions were carried out on a 1 mmol scale using 10 mol % of TP*Na, 10 mol % of CuCl, and 5 equiv of olefin in 2.7 mL of acetonitrile at room temperature under argon for 12 h. ^b Isolated yield. ^c This reaction performed using 10 mol % of DP*Na and 10 mol % of CuCl₂ as catalyst.

yields changed only modestly. It is worth noting that in those reactions which afforded more modest yields of the aziridination products, *p*-toluenesulfonamide was observed as a significant byproduct. The reasons for the different behaviors of these three classes of olefins are not yet clear and are the subject of ongoing investigations.¹²

In short, we have developed a new and convenient method for the efficient in situ generation of aziridination catalysts based on copper–poly(pyrazolyl)borate complexes. In these systems, there is a marked influence of the combination of the hapticity of the poly(pyrazolyl)borate and the starting oxidation state of copper on the reaction efficiency. The mechanistic rationale for this difference in reactivity is not clear and is currently the subject of ongoing investigations, the results of which will be reported in due course.

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(12) A possible rationale for the enhanced yield in the case of *trans*- β -methylstyrene using the DP catalyst instead of the TP catalyst would be that the increased steric bulk of the DP catalyst hinders coordination with the olefin, thus increasing nonproductive reaction pathways for the presumed copper–nitrene intermediate. The DP catalyst should be significantly less hindered and thus able to more efficiently coordinate with the olefin and lead to the desired aziridine product. However, in the presence of less hindered olefins (*cis* or terminal), the less hindered copper–nitrene intermediate with the DP catalyst results in increased nonproductive reaction pathways.