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Practical aziridinations II: electronic modifications to poly(pyrazolyl)borate–copper catalysts

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Abstract—A significant influence of the electronic features of poly(pyrazolyl)borate ligands on the efficiency of the copper-catalyzed aziridination reaction has been noted. Electron-deficient, bidentate di(pyrazolyl)borates in conjunction with copper(II) chloride generated the most effective catalyst system for the aziridination of a variety of olefins.

As part of an ongoing interest in practical, simple, catalytic methods for the preparation of organic building blocks, we have been particularly attracted to the challenge of preparing aziridines. The most straightforward synthetic strategy is the cycloaddition of an olefin with a nitrogen source,[1] which 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. Although similar difficulties with the use of carbenes have been largely resolved by the use of metal catalysts,[2] the same approach toward control of nitrene reactivity has not progressed to a synthetically advanced state.

This is not due to a lack of effort. A considerable number of catalyst systems have been reported, but they all have significant limitations.[3] One common issue is the relatively high catalyst loadings that are required (>5 mol %) to achieve optimal yields.[4] Another problem is that reaction yields are good for aryl-substituted olefins (such as styrene), but are unacceptably low for simple aliphatic olefins (such as cyclooctene). Part of the difficulty in solving these limitations is the limited (and frequently conflicting) mechanistic information regarding the metal-catalyzed aziridination reaction.[5] The other major limitation is that most currently employed catalyst systems are not readily tunable. Thus, factors such as steric and electronic effects can only be studied with great difficulty.

Our approach to this problem is to employ poly(pyrazolyl)borate–copper complexes as the aziridination catalyst.[6,7] The simplicity of preparing a wide range of modified poly(pyrazolyl)borate ligands combined with the stability of these species lends itself to the development of a practical, versatile catalytic system.[8] Indeed, we have already reported the use of in situ generated TP and DP complexes with copper as effective aziridination catalysts.[7] By tuning the hapticity of the ligand and the starting oxidation state of copper, a catalyst system was generated that was effective for the azidination of a variety of aryl-substituted olefins (Fig. 1). Unfortunately, the yields for aliphatic olefins remained low.

These initial studies made use of some of the flexibility afforded by the poly(pyrazolyl)borate skeleton. However, beyond the ability to vary the hapticity of the ligand, the poly(pyrazolyl)borates afford the opportunity to optimize the electronic effects of the ligand on the azidirination reaction. In particular, it seemed logical that less electron-rich poly(pyrazolyl)borate catalysts could be more active, since these species should be more Lewis acidic and thus better able to coordinate with the nitrene precursor and/or the olefin. Indeed, Dias and co-workers have observed that the

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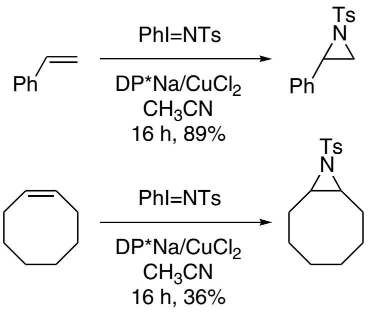


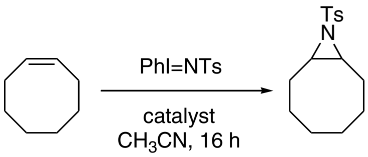
Figure 1. Aziridinations with in situ generated DP*CuCl.

tris[3,5-bis(trifluoromethyl)pyrazolyl]borate (TP^{F*}) ligand, in combination with metals such as copper, zinc, or silver, forms stable complexes with a variety of donor ligands including THF, DMF, and DMAC.[9]

Based on this precedent, the necessary DP and TP ligands were prepared using the standard literature procedures.[10] With these ligands in hand, their catalytic efficiency in the aziridination of cyclooctene was investigated (Table 1). As had been observed previously with styrene and the DP* and TP* systems, there was a small, but significant, effect of matching the ligand hapticity and the starting copper oxidation state (entries 1–4). This effect was also observed for the electron deficient poly(pyrazolyl)borate ligands (entries 5–8). More importantly, however, by matching the hapticity and oxidation state with the electron-deficient ligands, a significant improvement in the aziridination yield was observed. Thus, with the DP^{F*}Cu(II) Cl catalyst, the aziridination product of cyclooctene was isolated in 63% yield.

Armed with this promising observation, the DP^{F*}Na/CuCl$_2$ conditions were applied to other olefins. Aryl-substituted olefins generally afford good results with even the simple TP*Na/CuCl catalyst, and equally good results were obtained using the DP^{F*}Na/CuCl$_2$ system (Table 2).[11] Only in the case of 1,2-disubstituted olefins was a significant difference noted. Thus, both β-methylstyrene and dihydronaphthalene afforded much higher yields using the electron-deficient catalyst system than with the electron-rich DP*Na/CuCl$_2$ catalyst (entries 3 and 4).

Table 1. Aziridination studies on cyclooctene[a]



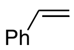
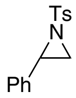
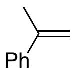
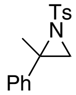
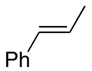
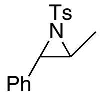
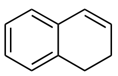
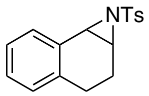
Entry	Catalyst	Yield[b] (%)
1	TP*Na/CuCl	44
2	TP*Na/CuCl$_2$	24
3	DP*Na/CuCl	30
4	DP*Na/CuCl$_2$	36
5	TP^F*Na/CuCl	43
6	TP^F*Na/CuCl$_2$	55
7	DP^F*Na/CuCl	37
8	DP^F*Na/CuCl$_2$	63

[a] All reactions were carried out on a 1 mmol scale using 10 mol % of the polypyrazolylborate salt, 10 mol % of copper chloride, and 5 equiv of olefin in 2.7 mL of argon-purged CH$_3$CN at rt.

[b] Isolated yield (average of three reactions).

A greater challenge is faced in the aziridination of alkyl-substituted olefins. Application of the same DP^{F*}Na/CuCl$_2$ reaction conditions afforded good to modest results for some simple olefins (Table 3).[11] Somewhat more strained olefins (pinene and cyclooctene) afforded higher isolated yields (50% and 63%, respectively), while a simple monosubstituted olefin (1-octene) afforded the lowest yield (20%). It is worth noting that in no case was any allylic amination product detected, even with cyclohexene, which is particularly prone to this mode of reactivity.[12]

Table 2. Aziridination of aryl-substituted olefins[a]

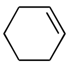
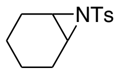
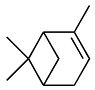
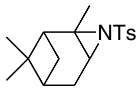
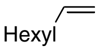
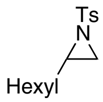
Entry	Olefin	Product	Yield[b] (%)
1			90
2			94
3			64 (46)[c]
4			96 (56)[c]

[a] All reactions were carried out on a 1 mmol scale using 10 mol % of sodium bis[3,5-bis(trifluoromethyl)pyrazolyl]borate, 10 mol % of copper(II) chloride, and 5 equiv of olefin in 2.7 mL of argon-purged CH$_3$CN at rt.

[b] Isolated yield (average of three reactions).

[c] Performed using DP*Na and CuCl$_2$ as the catalyst.

Table 3. Aziridination of alkyl-substituted olefins[a]

Entry	Olefin	Product	Yield[b] (%)
1			28
2			50
3			20

[a] All reactions were carried out on a 1 mmol scale using 10 mol % of sodium bis[3,5-bis(trifluoromethyl)pyrazolyl]borate, 10 mol % of copper(II) chloride, and 5 equiv of olefin in 2.7 mL of argon-purged CH$_3$CN at rt.

[b] Isolated yield (average of three reactions).

It certainly merits attention that even better results have been reported using isolated tri(pyrazolyl)borate copper(I) catalysts.[13] Thus, Dias has reported that the aziridination of cyclohexene with 5 mol % of the ethylene complex of copper(I) tris[3,5-bis(trifluoromethyl)pyrazolyl]borate affords the aziridination product in 93% yield. Interestingly, for 1-octene, their results are very similar to those obtained by us using the in situ generated catalyst (28% and 20%, respectively). Perez and co-workers have also used an isolated copper catalyst—copper(I) tris(2,3,4-tribromopyrazolyl)borate. At a 5 mol % loading, this system afforded very good yields, including a 91% yield for the aziridination of 1-hexene. As a result, these isolated catalysts appear to afford better results than our in situ generated catalysts, but they do require the preparation and isolation of the catalysts, which renders them a bit less convenient than our method.

In conclusion, utilizing the facile tunability of the poly(pyrazolyl)borate framework, we have discovered a new class of aziridination catalysts that employ less electron-rich ligands on the copper center. These catalysts are readily generated in situ from stable precursors and afford modest to excellent yields of the aziridine products from both aryl and alkyl-substituted olefins. Efforts are underway to develop a mechanistic understanding of the source of this enhanced activity as well as the combined influence of the ligand hapticity and the starting copper oxidation state. These efforts will be reported in due course.

Acknowledgements

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