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Palladium-Catalyzed Enantioselective C–H Activation of Aliphatic Amines Using Chiral Anionic BINOL-Phosphoric Acid Ligands

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Supporting Information

ABSTRACT: The design of an enantioselective Pd(II)-catalyzed C–H amination reaction is described. The use of a chiral BINOL phosphoric acid ligand enables the conversion of readily available amines into synthetically valuable aziridines in high enantiomeric ratios. The aziridines can be derivatized to afford a range of chiral amine building blocks incorporating motifs readily encountered in pharmaceutically relevant molecules.

The development of catalytic enantioselective aliphatic C–H functionalization processes represents an important challenge for chemical synthesis.[1] Most prominent among the successful advances toward this ideal has been the use of metallocarbenoid and -nitrenoid strategies.[2] In contrast, processes that are based on enantioselective metal insertion into aliphatic C–H bonds remain limited.[3] Part of the reason for this deficiency is the lack of available chiral ligands that are effective for oxidative C–H functionalization with catalysts derived from Pd(II) salts. The most common classes of ligand for metal-catalyzed enantioselective reactions, chiral phosphines,[3] are generally incompatible with the reaction conditions required for oxidative Pd-catalyzed C–H functionalization. As a result, the design of novel classes of ligands for Pd(II) catalysts has been the focus of significant attention in the synthetic community (Figure 1a).[4]

The catalytic enantioselective desymmetrization of prochiral methyl groups via Pd-catalyzed Csp^3–H activation represents a potentially useful strategy for the generation of compounds displaying nonracemic fully substituted carbon atoms. Enantioselective desymmetrization of prochiral methyl groups has been successfully achieved using Pd(0)-catalyzed methods; Kagan, Baudoin, Kundig, and Cramer have all reported variations on a C–H amination to indolines.[3] Less common are successful examples of enantioselective oxidative C–H desymmetrization using Pd(II)-catalysts. For example, Yu et al. have reported a Pd(II)-mediated, auxiliary-controlled disatereoselective C–H iodination of oxazolines,[4a] and Pd(II)-catalyzed C–H functionalizations controlled by amino acid based ligands that give moderate but promising levels of enantioselectivity for alkylation and arylation.[4b,c] Related to this, our own efforts identified that similar amino acid derived ligands enable Pd(II)-catalyzed enantioselective arylation of tetramethylpiperidine with moderate enantioselectivity.[5c]

Our laboratory has been engaged in the development of a series of processes for the Pd-catalyzed C–H functionalization of free(NH) aliphatic amines.[5] Central to the success of many of these reactions has been a putative hydrogen bond between the

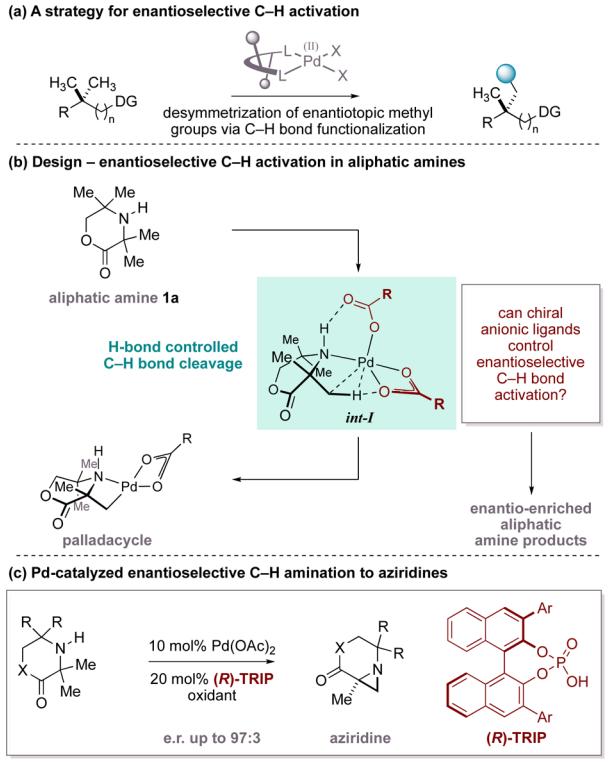

Figure 1. A strategy toward anionic ligand-controlled enantioselective Pd-catalyzed C–H activation.

NH motif of a ligated amine and the carbonyl oxygen atom of the Pd-bound carboxylate.[5b] For example, in the case of tetramethylmorpholinone **1a**, a hydrogen bond helps to arrange the C–H bond into the ideal orientation for activation with a second Pd-bound carboxylate (***int-I***, Figure 1b). Based on this, we reasoned that deployment of a chiral carboxylate or related anionic ligand might lead to a scenario wherein the irreversible C–H cleavage step would be rendered enantioselective via the desymmetrization of two prochiral methyl groups, leading ultimately to nonracemic aliphatic amine products.

The use of chiral anionic ligands to control enantioselective C–H activation with Pd catalysts has only recently received attention. Aside from the deployment of chiral amino acid derivatives,[4] Duan et al. have described the use of BINOL-derived phosphoric acids[6,7] to impart modest enantioselectivity

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Table 1. Selected Optimization Data for Enantioselective Pd-Catalyzed C−H Amination to Aziridines

entry	$Pd(OAc)_2$, mol %	(*R*)-TRIP, mol %	solvent	oxidant	additives/comments	concn, M	yield (GC)	e.r. (GC)
1	5	5 (of **3a**)	PhMe	PIDA	–	0.1	16	53:47
2	5	5	PhMe	PIDA	–	0.1	65	55:45
3	5	5	EtOAc	PIDA	–	0.1	64	79:21
4	5	5	EtOAc	PIDA	2 equiv of Ac_2O	0.1	75	78.5:21.5
5	5	5	EtOAc	PIDA	20 equiv of AcOH	0.1	82	52:48
6	5	5	EtOAc	PIDA	–	0.05	71	84:16
7	5	10	EtOAc	PIDA	–	0.05	67	89:11
8[a]	**10**	**20**	**EtOAc**	**PIDA**	**0.5 equiv of Ac_2O**	**0.05**	**79**	**93.5:6.5**
9	5	5	EtOAc	PhI=O	–	0.1	10	86:14
10	5	10	EtOAc	I_2	0.5 equiv of Ac_2O	0.05	4	95:5
11	5	10	EtOAc	I_2, AgOAc		0.05	86	95:5
12[b]	**10**	**20**	**EtOAc**	**I_2, AgOAc**	**90 °C**	**0.033**	**88**	**96.5:3.5**

[a]Condition A. [b]Condition B.

in a methylene C−H arylation reaction.[8] Based on this seminal discovery, two further reports detailing chiral BINOL-phosphates as effective ligands for enantioselective C−H activation recently emerged; Yu et al. detailed a highly selective enantiotopic methylene C−H arylation in thioamide derivatives,[9a] and Chen et al. reported an auxiliary-directed C−H arylation of amide derivatives.[9b] Here, we report our own studies on the use of a BINOL-phosphoric acid derivative,[6] as a chiral anionic ligand,[7] to enable the Pd-catalyzed enantioselective C−H amination of aliphatic amines to form aziridines. High enantioselectivities and yields are obtained for the aziridination process, and the products of the reaction can be readily transformed into novel variants of privileged saturated amine hetereocycles, which we believe will be of significant interest to practitioners of medicinal chemistry (Figure 1c).

At the outset of our studies, we tested the enantioselective C−H amination of morpholinone **1a**, to give aziridine **2a**, by screening a range of chiral acids in combination with 5 mol % $Pd(OAc)_2$ and phenyliodosyldiacetate (PIDA) in toluene at 70 °C (see Supporting Information for details). Unfortunately, none of these reactions resulted in significant enantioselectivity in the product. However, we did find that when 5 mol % of BINOL-derived phosphoric acid (BPA, **3a**) was added to the reaction, a 16% yield and a low enantiomeric ratio (e.r.) of 53:47 were observed (Table 1, entry 1). Based on this, we tested the 3,3′-diaryl-BINOL phosphoric acid, (*R*)-TRIP **3b**, under the same conditions and found that although the e.r. had risen slightly to 55:45, the yield was improved to 70% (entry 2). A screen of solvents revealed an improved reaction in EtOAc, which increased the e.r. of the product to 79:21 with a moderate yield (entry 3). The addition of 2 equiv of Ac_2O did not significantly affect the reaction (entry 4). We also found that the addition of 20 equiv of AcOH, found to be beneficial in the racemic reaction,[5b] reduced the reaction to an almost racemic process, albeit in high yield (entry 5). Reducing the concentration to 0.05 M increased the yield of the product to 71% and the e.r. to 84:16 (entry 6). We next increased the amount of (*R*)-TRIP in the reaction to maximize the formation of the chiral-Pd catalyst, thereby minimizing any nonchiral background reaction involving $Pd(OAc)_2$; using 10 mol % of (*R*)-TRIP with 5 mol % $Pd(OAc)_2$ gave an e.r. of 89:11 with a 67% yield of **2a** (entry 7). Increasing the loading of $Pd(OAc)_2$ to 10 mol %, combined with 20 mol % of (*R*)-TRIP and the addition of 0.5 equiv of Ac_2O, gave a 79% yield of the product with an e.r. of 93.5:6.5 (entry 8, Condition A). To the best of our knowledge, this represents the first example of a highly enantioselective Pd(II)/Pd(IV)-catalyzed process for desymmetrizing C−H functionalization of prochiral methyl groups.

We were conscious that using PIDA as an oxidant generates 2 equiv of AcOH, whose increasing concentration throughout the reaction may compromise the enantioselectivity of the process (entry 5). Accordingly, we found that use of "acetate-free" oxidants such as iodosylbenzene or iodine[4a,10] resulted in an improved enantiomeric ratio of 86:14 and 95:5 respectively, but the yields were dramatically reduced (entries 9, 10).[11] Multiple oxidants were investigated in order to attain catalytic turnover, and it was found that addition of AgOAc improved the yield and maintained the e.r. of the product (entry 11). After further optimization of the reaction parameters (lowering concentration, increasing catalyst loading, and increasing temperature) we found that an 88% yield of aziridine product with an e.r. of 96.5:3.5 could be obtained (entry 12, Condition B). It is clear that the enantioselectivity depends on a delicate balance between the concentration of AcOH and the chiral TRIP ligand, suggesting that AcO^- can replacing the TRIP ligand on the Pd(II) center at high concentrations of AcOH, leading to racemic turnovers. Therefore, it is possible that using 20 mol % of the TRIP ligand offsets this problem, particularly toward the end of the reaction. Furthermore, by using AgOAc, which is heterogeneous in this reaction, we suggest that its insolubility is beneficially modulating the concentration of AcO^-/AcOH.[12] Taken together, the optimization studies revealed two sets of reaction conditions (A and B).

With optimal conditions in hand, we explored the scope of the Pd-catalyzed enantioselective C−H amination (Table 2). First, we assessed simple derivatives of the morpholinone scaffold and found that variations at both sides of the free(NH) amine were accommodated. In addition to the tetramethyl morpholinone **1a**, a cyclohexyl-derived substrate worked effectively in the reaction giving a 95:5 enantiomeric ratio in aziridine **2b** with moderate yield. We were pleased to observe that methylene C−H amination to the spirocyclic aziridine **2c** was also successful with an excellent e.r. of 94.7:5.3, the low yield being comparable to that of the racemic reaction. Aziridine **2c** was also crystalline, enabling determination of its absolute configuration via X-ray diffraction. We also investigated the corresponding piperazinone scaffold, wherein the heterocyclic oxygen of the morpholinone is replaced by a nitrogen containing group; successful C−H activation on these substrates would substantially broaden the scope of the reaction and provide access to medicinally relevant heterocyclic products. We were pleased to find that a series of functionalized *N*-alkyl derivatives containing benzyl, glycinyl,

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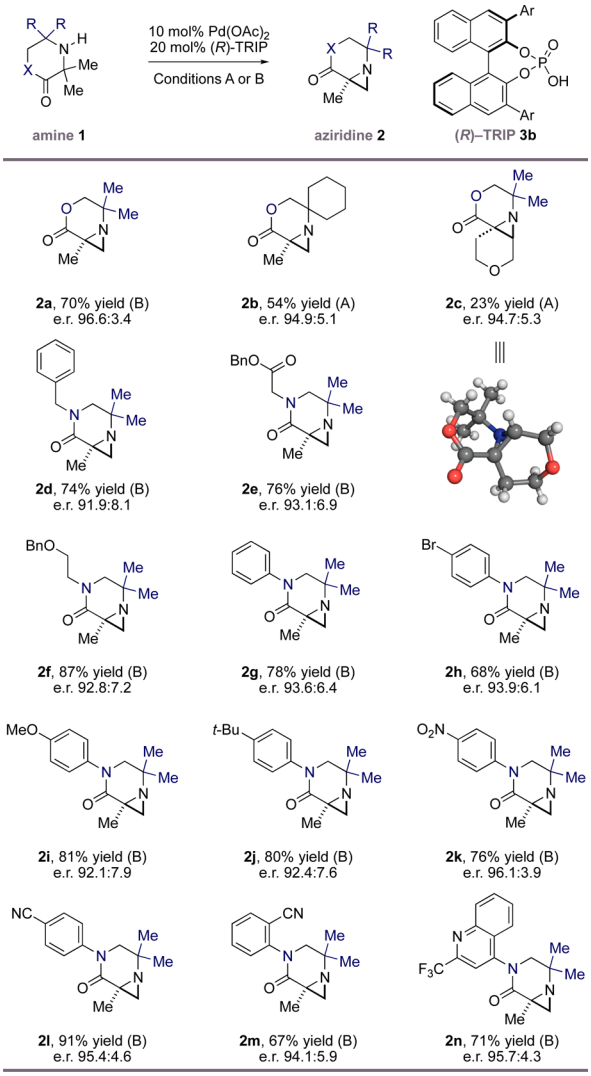
Table 2. Scope of Enantioselective C−H Amination[a]



[a]Conditions A: Substrate (1.0 equiv), 10 mol % $Pd(OAc)_2$, $PhI(OAc)_2$ (2.5−4.0 equiv), Ac_2O (0.5 equiv), 20 mol % (*R*)-TRIP, EtOAc (0.05 M). Conditions B: Substrate (1.0 equiv), 10 mol % $Pd(OAc)_2$, AgOAc (3.0 equiv), I_2 (2.0 equiv), 20 mol % (*R*)-TRIP, EtOAc (0.033 M). Yields are quoted after flash column chromatography. Chiral analysis was carried out using GC or HPLC.

and hydroxylethyl motifs all worked well in the reaction, delivering the aziridines **2d−f** in good yield and high e.r.'s. N-Aryl substrates also worked well in the reaction and a range of electronic and steric properties were tolerated, with electron-rich (**2g−j**), electron-deficient (**2k−m**), and even Lewis basic heterocyclic motifs (**2n**) all providing the corresponding aziridines in good yields and high e.r.'s.

Interestingly, we noticed a variation in e.r. depending on the electronic properties of the N-aryl group in amines **2g−l**. When the log(e.r.) of the aziridines is plotted against the Hammett σ constant of the aryl substituent, one can draw a linear correlation between the enantioselectivity and electronic properties of the group (Figure 2).[13] Furthermore, it is noticeable that the e.r.'s in the corresponding morpholinones are higher than the lactam series, possibly reflecting the more electronegative nature of the lactone oxygen atom.

In considering the pathway through which this enantioselective transformation proceeds, it was important to rationalize

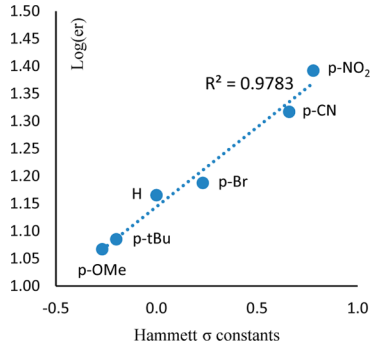


Figure 2. Correlation between e.r. and Hammett constant.

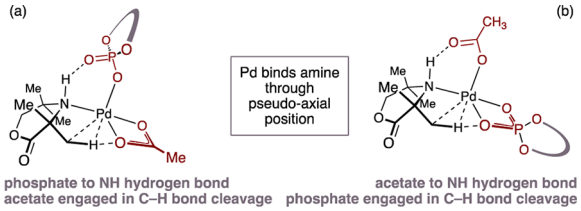


Figure 3. Possible pathways for the enantioselective C−H activation.

the apparent impact of acetate concentration on the reaction. An explanation for this effect could invoke an active Pd(II) complex displaying one acetate and one TRIP ligand. It seems unlikely, based on the size of TRIP, that two of these ligands could be accommodated around the Pd(II) center; attempts to synthesize $Pd(TRIP)_2$ were unsuccessful.

We have previously shown that the Pd(II)-catalyst coordinates the free(NH) of the amine through the nitrogen lone pair in the pseudoaxial position,[5b] which means that the subsequent C−H activation is only possible at the methyl group that is syn to the coordinated metal (pseudoequatorial on the ring), leading to the four-membered ring cyclopalladation complex. As a result, one scenario could involve a hydrogen bond between the NH and the phosphate ligand, providing a rigid transition structure for C−H cleavage via a concerted-metalation−deprotonation type pathway utilizing the acetate group (Figure 3a).[14] A second possibility involves an acetate hydrogen bonding to the ligated amine and the irreversible and enantiodetermining C−H cleavage mediated by the phosphate ligand (Figure 3b). While these models lay out a preliminary understanding of the factors that influence this reaction, it was not possible, at this stage, to further elucidate which pathway is prevalent or the nature of the enantioselectivity observed in this reaction.[15] Computational studies to elucidate the stereocontrolling elements of this catalyst−ligand combination are ongoing and will be reported in due course.

We previously demonstrated that the aziridine ring in the morpholinone-derived products could be opened in the presence of nucleophiles. To test whether the corresponding lactam-aziridines were also compatible with this ring opening transformation, we subjected **2d** to treatment with pyrazole in the presence of *p*-toluenesulfonic acid to reveal the amide product in 72% yield (Scheme 1). Reduction of the lactam was achieved using $LiAlH_4$ in THF to afford highly substituted piperazine **4** in good yield. We also showed that, after opening **2d** with MeOH, a second diastereoselective C−H amination takes place to form aziridine **5** in good yield. Aziridine ring opening with pyrazole and subsequent lactam reduction affords piperazine **6** in good yield. We believe that these nonracemic highly functionalized saturated amine heterocycles would be difficult to form by other

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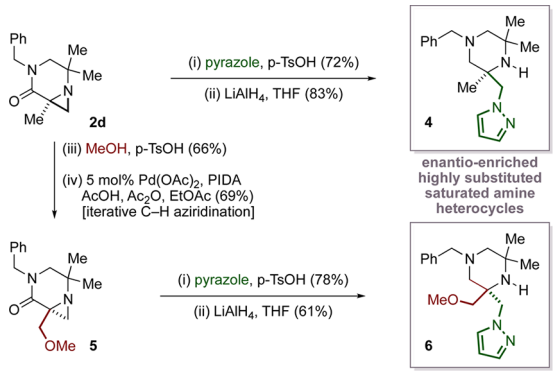
Scheme 1. Synthesis of Complex Amines



methods and should be attractive building blocks in medicinal chemistry programs.[16]

In conclusion, we have developed a Pd-catalyzed enantioselective C−H amination to aziridines using anionic BINOL phosphate ligands. A range of amines, displaying prochiral methyl groups, undergo enantioselective desymmeterizing C−H activation to produce highly substituted and functionalized products that can be transformed into nonracemic saturated heterocyclic building blocks. While the precise nature of the enantiocontrol imparted by the TRIP ligands remains unclear, we believe that this asymmetric C−H activation process will be of significant utility to practitioners of synthetic and medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b12234.

Experimental procedures and spectral data (PDF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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