

Palladium-Catalyzed Enantioselective (2-Naphthyl)methylation of Azaarylmethyl Amines

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Palladium-Catalyzed Enantioselective (2-Naphthyl)methylation of Azaarylmethyl Amines

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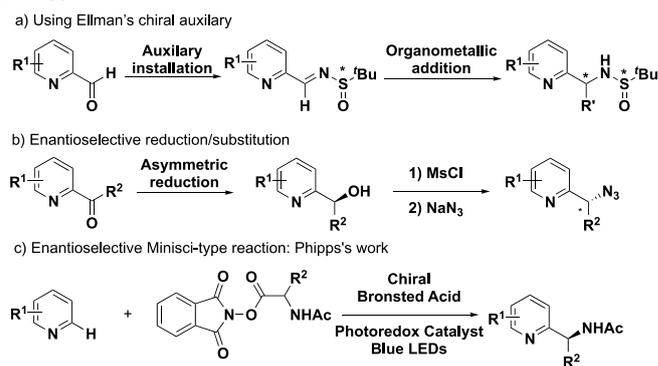
Enantioenriched azaarylmethyl amine derivatives are useful building blocks in synthetic and medicinal chemistry. To access these valuable motifs, an enantioselective palladium-catalyzed benzylation of azaarylmethyl amine pronucleophiles is introduced. Of note, this is a rare application of asymmetric (2-naphthyl)methylation of pro-nucleophiles with high pK_a values ($pK_a \approx 34$ in DMSO). Control experiments support the notion that the coordination of Li^+ to the azaaryl nitrogen plays a critical role in the substitution process. With this procedure, enantioenriched (2-naphthyl)methylene azaarylmethyl amines with a variety of azaaryl groups (pyridyl, pyrazine, quinoxaline and isoquinoline) and cyclic and acyclic amines are readily obtained with good yields and enantioselectivities up to 99%.

Introduction

Nitrogen containing aromatic compounds are widespread in small-molecule drugs, pharmaceuticals, agrochemicals and natural products.^{1–6} Among nitrogen containing compounds, azaarylmethyl amines frequently exhibit bioactivity, including antitumor,⁷ antihistamine⁸ and anti-HIV properties.⁹ The preparation of enantioenriched α -azaarylmethyl amines has been inspired, in part, by a drive from the pharmaceutical industry to increase the number of amino groups in molecules to be tested for bioactivity.¹⁰ Furthermore, enantioenriched pyridyl amines have been gaining momentum as ligands in asymmetric catalysis.^{11–16} The increased interest in enantioenriched α -azaarylmethyl amines has led to a variety of methods for their synthesis. Typical strategies to install the acyclic stereocenter at the benzylic position of azaaryl derivatives include diastereoselective additions of organometallics to Ellman's sulfinimine (Scheme 1a).^{17–19} Another approach involves asymmetric hydrogenation of azaaryl ketones to enantioenriched α -azaarylmethyl alcohols, which are sulfonated and treated with azide to form organic

azide products that retain high levels of ee (Scheme 1b).^{20, 21} The resulting azides can then be reduced to the amines. These routes to prepare chiral azaaryl amines require introduction and removal of auxiliaries or further manipulation of functional groups. An elegant method to synthesize chiral azaarylmethyl amine derivatives based on cooperation of a Brønsted acid with a photoredox catalyst has been reported by the groups of Phipps and Jiang (Scheme 1c).^{22, 23} The catalytic enantioselective Minisci-type reaction is highly attractive for the synthesis of azaarylmethyl amines. Ideally the scope of this reaction can be broadened beyond pyridines, quinolines and isoquinolines.

Scheme 1. Strategies to access enantioenriched heterocyclic amines



We envisioned that nucleophilic attack on η^3 -benzyl-type intermediates could be potentially useful in the construction of enantioenriched azaarylmethyl amines. Compared with Pd-catalyzed asymmetric allylic alkylations,^{24–35} enantioselective benzylic alkylations are far less common.³⁶ This is likely due to the greater difficulty forming the initial arene intermediate, (LG- $CH_2C_6H_5$)-Pd(0), and the subsequent oxidative ionization of the leaving group with concomitant disruption of aromaticity.^{37, 38}

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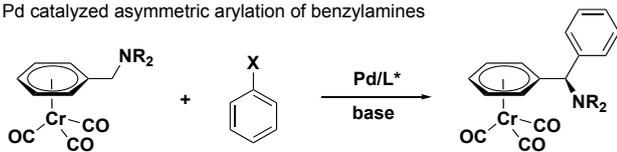
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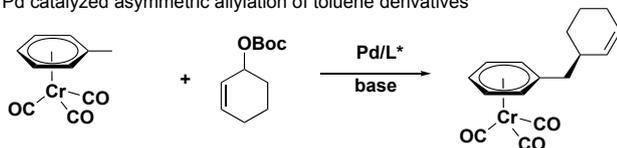
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Scheme 2. Our previous work (a-c) on the asymmetric functionalization of weakly acidic C–H's and this work (d).

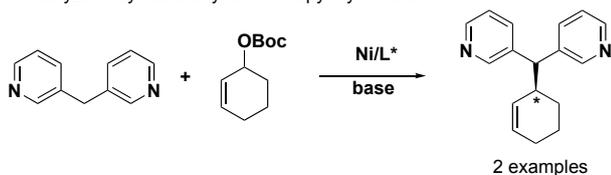
a) Pd catalyzed asymmetric arylation of benzylamines



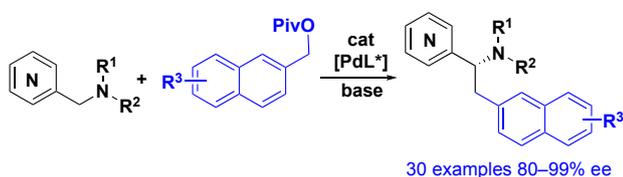
b) Pd catalyzed asymmetric allylation of toluene derivatives



c) Ni catalyzed asymmetric allylation of dipyriddy methane

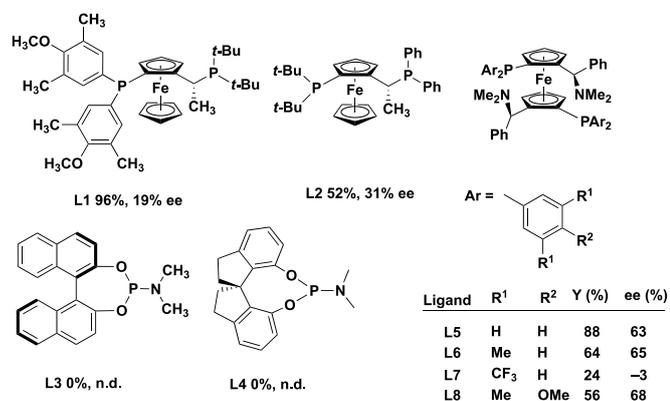
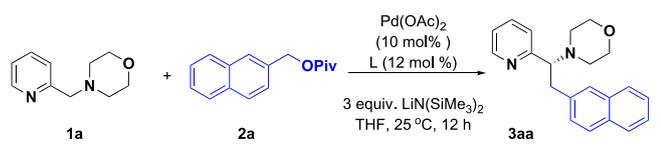


d) This work - Pd catalyzed asymmetric benzylation of 2-azaarylmethyl amines



Most of the nucleophiles employed in asymmetric benzylations are organozinc³⁹ and organoboron reagents.⁴⁰ Other strategies employ enolate derived nucleophiles^{41, 42} or decarboxylative benzylations.^{43, 44} To the best of our knowledge, there are no benzylations or (2-naphthyl)methylations reported that involve weakly acidic C–H pro-nucleophiles with pK_a values as high as 34 (in DMSO).^{45, 46} Our team has a long history of using weakly acidic pro-nucleophiles with deprotonation in situ to perform C–C bond formations. For example, we have

Scheme 3. Ligand effects in asymmetric (2-naphthyl)methylation.



[a] Reaction conditions: **1a** (0.05 mmol), **2a** (0.15 mmol), Base (0.15 mmol), 10 mol% Pd 12 mol% Ligand L8, 0.1 M, 12 h. [b] Yields were determined by the ¹H NMR with CH₂Br₂ as internal standard. [c] The ee values were determined by HPLC. [d] 5 mol% Pd₂(dba)₃. THF = tetrahydrofuran, DME = 1,2-dimethoxy ethane, Piv = Pivaloyl, Boc = *tert*-butyloxycarbonyl.

realized the asymmetric arylation and allylation of benzylamines and toluene derivatives activated by the π -acidic Cr(CO)₃ moiety (Schemes 2a–b).⁴⁷ Initial results in the asymmetric allylation of 3,3'-dipyridylmethane (Scheme 2c) have also been realized. Based on these precedence, and the utility of enantioenriched α -azaarylmethyl amines,^{48–50} we set out to develop the asymmetric benzylation of azaarylmethyl amines ($pK_a \approx 34$ in DMSO).⁴⁵ Herein we describe the successful development of a new palladium catalyzed C–H functionalization of the α -position of tertiary amines to prepare α -azaarylmethyl amines in up to 98% yield and 98% ee.

Table 1 Optimization of the Reaction Conditions.^[a]

Entry	Pd	T (°C)	X	Base	Solvent	Yield ^[b] (%)	ee ^[c] (%)
1	Pd(OAc) ₂	25	OPiv	LiN(SiMe ₃) ₂	THF	56	68
2	Pd(COD)Cl ₂	25	OPiv	LiN(SiMe ₃) ₂	THF	72	76
3	Pd(acac) ₂	25	OPiv	LiN(SiMe ₃) ₂	THF	66	79
4 ^[d]	Pd ₂ (dba) ₃	25	OPiv	LiN(SiMe ₃) ₂	THF	66	80
5	Pd(dba) ₂	25	OPiv	LiN(SiMe ₃) ₂	THF	74	79
6	Pd(dba) ₂	0	OPiv	LiN(SiMe ₃) ₂	THF	72	90
7	Pd(dba) ₂	0	OBoc	LiN(SiMe ₃) ₂	THF	71	90
8	Pd(dba) ₂	0	OAc	LiN(SiMe ₃) ₂	THF	trace	trace
9	Pd(dba) ₂	0	OPiv	NaN(SiMe ₃) ₂	THF	trace	–
10	Pd(dba) ₂	0	OPiv	KN(SiMe ₃) ₂	THF	trace	–
11	Pd(dba) ₂	0	OPiv	LiN(SiMe ₃) ₂	DME	72	93
12	Pd(dba) ₂	0	OPiv	LiN(SiMe ₃) ₂	TBME	62	90
13	Pd(dba) ₂	0	OPiv	LiN(SiMe ₃) ₂	<i>i</i> -Pr ₂ O	56	60

[a] Reaction conditions: **1a** (0.05 mmol), **2a** (0.15 mmol), Base (0.15 mmol), 10 mol% Pd 12 mol% Ligand L8, 0.1 M, 12 h. [b] Yields were determined by the ¹H NMR with CH₂Br₂ as internal standard. [c] The ee values were determined by HPLC. [d] 5 mol% Pd₂(dba)₃ crystallized from benzene. THF = tetrahydrofuran, DME = 1,2-dimethoxy ethane, Piv = Pivaloyl, Boc = *tert*-butyloxycarbonyl.

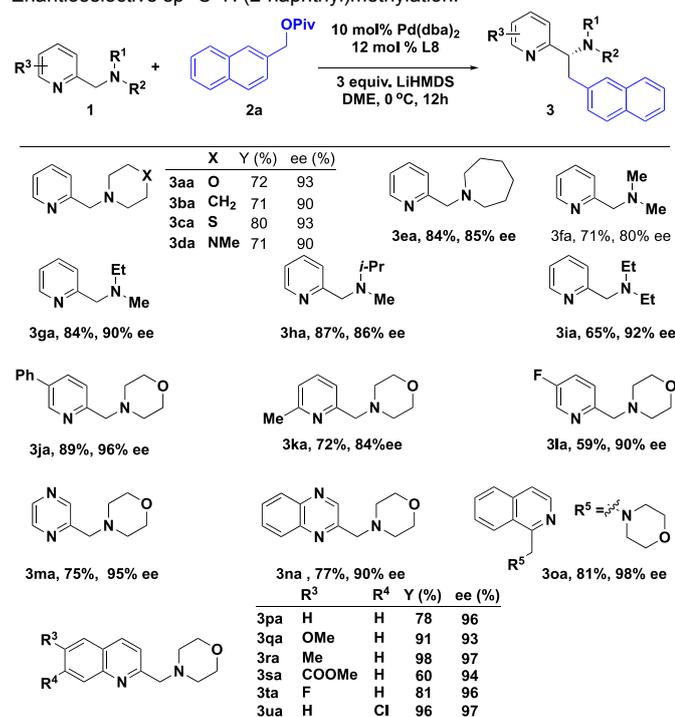
We initiated the asymmetric (2-naphthyl)methylation of 4-(pyridin-2-ylmethyl)morpholine **1a** by testing 54 common enantioenriched mono- and bidentate phosphine ligands with Pd(OAc)₂, lithium bis(trimethylsilyl)amide and pivalate **2a** at room temperature (see Supporting Information for details). In general, bidentate phosphine ligands performed better, and Mandyphos (**L5**) was the most promising initial hit with 88% yield and 63% ee. The enantioselectivity was improved to 68% with ligand **L8** possessing electron donating methoxy groups (Scheme 3, Table 1, entry 1). With this lead in hand, various Pd sources were examined, including (COD)PdCl₂, Pd(acac)₂, Pd₂(dba)₃, and Pd(dba)₂ which provided the desired product with ee values between 76%–80% and yields of 66%–74% (Table 1, Entries 2–5). Pd(dba)₂ was the best Pd source based on

product yield and ee. We were pleased to find that lowering the reaction temperature to 0 °C led to improvement of the enantioselectivity to 90% (Table 1, Entry 6).⁵¹ Replacing the leaving group OPiv with OBoc led to similar results, but the less reactive OAc resulted in only trace product (Table 1, Entries 7–8).⁵² To our surprise, the reaction failed when the more reactive NaN(SiMe₃)₂ and KN(SiMe₃)₂ were employed (Table 1, Entries 9–10).⁵³ These results led us to speculate that binding of the lithium cation to the 2-pyridyl nitrogen plays a critical role in this substitution process. Next, solvents DME, *tert*-butyl methyl ether and di-*iso*-propyl ether were examined (Table 1, Entries 11–13) and DME was found to give the same yield as THF but with slightly higher ee (93%).

With the optimized conditions in hand (Table 1, Entry 11), we focused on investigating the scope of pyridine-based pro-nucleophiles with naphthalen-2-ylmethyl pivalate (**2a**) as the electrophile (Scheme 4). It is noteworthy that pyridines are the most prevalent nitrogen heterocycles in medications.^{2, 54} Pyridyl-based azaarylmethyl amines incorporating various six membered rings, including morpholine (**1a**), piperidine (**1b**), thiomorpholine(**1c**) and *N*-methylpiperazine (**1d**) proved to be compatible with the catalytic reactions and gave the (2-naphthyl)methylation products **3aa–3da** in good yields (71–80%) and excellent ee values (90–93%). The azepane derivative **1e** afforded the coupling products **3ea** in 84% yield with 85% ee. Acyclic dialkyl amines **1f–1i** with varying degrees of steric hinderance about the amino group were suitable coupling partners and provided the expected products **3fa–3ia** in 65–87% yield and 80–92% ee.

Next, substitutions on the 2-pyridyl group were examined. The 5-phenyl substituted adduct **3ja** was isolated with 89% yield and 96% ee. Substrate **1k**, with a methyl group underwent the

Scheme 4 Scope of Azaarylmethyl Amines in the Palladium Catalyzed Enantioselective sp³ C–H (2-naphthyl)methylation.^[a]



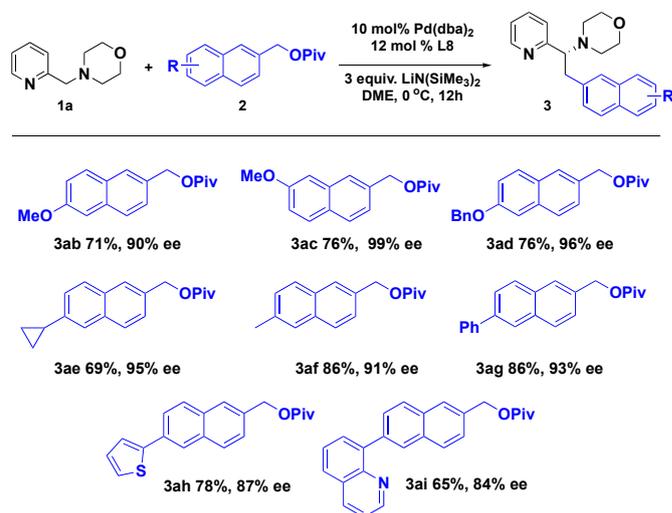
[a] Reaction conditions: **1a** (0.05 mmol), **2a** (0.15 mmol), Base (0.15 mmol), 10 mol% Pd 12 mol% Ligand L8, 0.1 M, 12 h. [b] Yields are isolated yields. [c] The ee values were determined by HPLC. [d] 5 mol% Pd₂(dba)₃. THF = tetrahydrofuran, DME = 1,2-dimethoxy ethane, Piv = Pivaloyl, Boc = *tert*-butyloxycarbonyl.

(2-naphthyl)methylation reaction with 72% yield and 84% ee. Product from deprotonation of the methyl group was not observed. The fluoro-substituted pro-nucleophile **1l** was a suitable coupling partner and resulted in formation of **3la** in 59% yield and 90% ee.

Heterocycles beyond pyridines were next examined. Amines bearing pyrazine (**1m**), quinoxaline (**1n**) and isoquinoline (**1o**), were competent coupling partners and afforded the corresponding adducts **3ma–3oa** in 75–81% yield and 90–98% ee. Quinoline-based methyl amines, including the parent compound (**1p**) and those bearing methoxy (**1q**), methyl (**1r**), ester (**1s**), fluoro (**1t**), and chloro (**1u**) were tolerated under our conditions and afforded the corresponding (2-naphthyl)methylation products **3pa–3ua** in 60–98% yield with ee values of 93–97%.

The scope of the electrophile was next examined, as shown in Scheme 5. Naphthalen-2-ylmethylpivalates supporting 6-methoxy (**2b**) or 7-methoxy (**2c**) substituents both underwent the (2-naphthyl)methylation and furnished adducts **3ab** and **3ac** in 71% and 76% yield and 90% and 99% ee, respectively. Substrate **2d**, with an appended benzyl ether was a suitable coupling partner and resulted in formation of **3ad** in 76% yield and 96% ee. Cyclopropyl groups are frequently found in bioactive compounds.⁵⁵ The cyclopropyl substituted electrophile **2e** was compatible with the process and gave the target product **3ae** in 69% yield and 95% ee. Substrates bearing a methyl (**2f**) or phenyl (**2g**) participated in the coupling to generate **3af** in 86% yield and 91% ee and **3ag** in 86% yield and 93% ee. Electrophiles containing the 2-thiophenyl and 8-quinolinyl heteroaromatic groups **2h** and **2i**

Scheme 5 Scope of Naphthalen-2-ylmethyl pivalate in Palladium Catalyzed Enantioselective sp³ C–H (2-naphthyl)methylation.^[a]



[a] Reaction conditions: **1a** (0.05 mmol), **2** (0.15 mmol), LiN(SiMe₃)₂ (0.15 mmol), 10 mol% Pd(dba)₂, 12 mol% Ligand, 0.1 M, 12h, 0 °C.

furnished adducts **3ah** and **3ai** in 78% and 65% yield with 87% and 84% ee, respectively.

In order to demonstrate the utility of this method, we increased the scale ten-fold to 0.5 mmol further and increased it to 4.4 mmol with the amine **1p** as nucleophile and pivalate **2c** as electrophile (Scheme 6). The benzylation reaction afforded

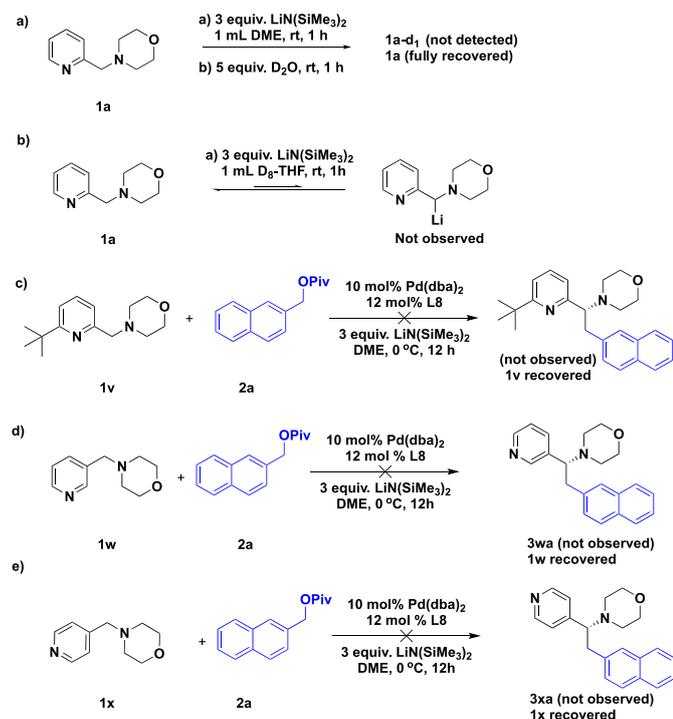
the product **3pc** in 74% and 72% yield with 85% and 87% ee. Crystals suitable for X-ray crystallographic analysis were obtained of **3pc** and the absolute configuration of the tertiary amine was found to be (*R*) (CCDC 2107204, see the Supporting Information for details).

Scheme 6 Scale up of the Palladium Catalyzed Enantioselective sp^3 C–H (2-Naphthyl)methylation.



A few experiments were conducted to gain insight into the substitution process. Benzylic deprotonation of the 2-azaaryl methyl amine is a key step in the asymmetric coupling, causing us to wonder to what extent it might be deprotonated under conditions to simulate the reactions outlined herein. Thus, we subjected **1a** to 3 equiv $LiN(SiMe_3)_2$ for 1 h at rt, then quenched the reaction with D_2O . No incorporation of deuterium into the product was detected by 1H NMR analysis of the quenched product. Consistent with this observation, conducting a similar deprotonation in $THF-d_8$ at rt for 1 h before acquiring the 1H NMR spectrum of the mixture also showed only unreacted **1a** without noticeable formation of the organolithium. These results suggest that the deprotonation equilibrium lies far to the side of the pro-nucleophile **1a**. Of course, only a small amount of deprotonated material is necessary to drive the reaction.

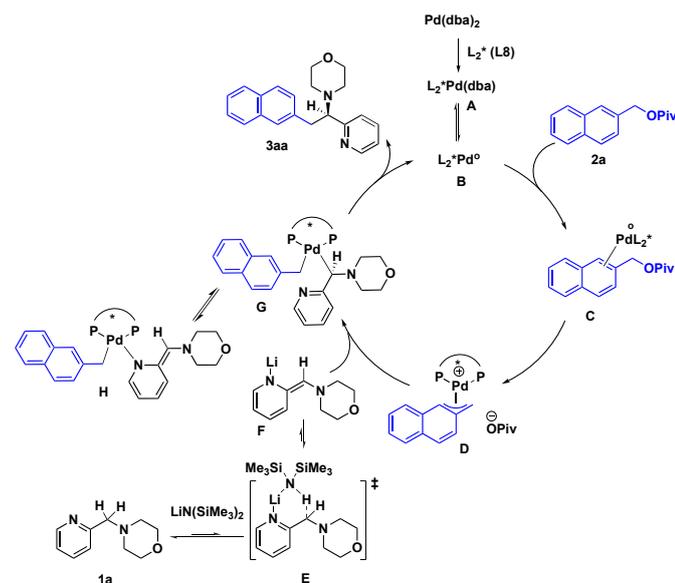
Scheme 7 Control experiments



As noted earlier, the nature of the cation in $MN(SiMe_3)_2$ was found to play an important role in governing the overall reactivity. Because the more reactive bases $NaN(SiMe_3)_2$ and $KN(SiMe_3)_2$ both failed to afford the target tertiary amine (Table 1, Entries 9–10) we suspected that coordination of the Li^+ to the azaaryl nitrogen was necessary. We therefore examined substrate **1v** containing a 2-*tert*-Bu group adjacent to the nitrogen to inhibit binding of the Li^+ to N (Scheme 7a). The *tert*-Bu group turned off the reaction with $LiN(SiMe_3)_2$, consistent with our hypothesis that binding of Li^+ to N is important. Next, the 3-pyridyl- and 4-pyridylmethyl amines were tested as pro-nucleophiles. Although neither pyridyl nitrogen in these substrates can coordinate to lithium and facilitate deprotonation, it should be noted that benzylic hydrogens situated at the 4-position of pyridines are more acidic than those at the 2-position.⁴⁶ In other words, **1x** is more acidic than **1a** and should be more easily deprotonated if pre-coordination is not a prerequisite. In the event, neither **1w** or **1x** participated in the (2-naphthyl)methylation under the standard conditions. In these cases, starting materials were recovered (Schemes 7d–e). These experimental results support our suspicions about the importance of Li^+ binding to the basic 2-pyridyl nitrogen.

Based on the above results, we postulate a possible reaction pathway (Scheme 8). Starting with $Pd(dba)_2$ at the top of Scheme 8, ligand exchange with the bidentate phosphine ligand generates $L_2^*Pd(dba)$ (**A**), which loses *dba* to give unsaturated $L_2^*Pd^0$ (**B**, where L_2 represents the bidentate phosphine). Coordination of the Pd to the arene π -system to give **C** is followed by oxidative ionization of the benzylic pivalate to give Pd(II) intermediate **D**.⁵⁶ Meanwhile, the pro-nucleophile **1a** coordinates to the lithium of $LiN(SiMe_3)_2$ and is deprotonated via the transition state **E** to give the organolithium **F**. The organolithium **F** undergoes transmetalation to generate palladium complex **G**. Complex **G** can undergo epimerization by migration of the palladium to the nitrogen as in **H** and back to carbon. We speculate that the diastereomers of **G** (only one shown) will have different energies and will undergo reductive elimination with different barriers, resulting in the observed enantiomeric excess of **3aa**. There are other possible mechanisms that cannot be excluded here. One is that the π -benzyl will undergo attack by the nucleophilic organolithium from opposite the palladium (attack on a coordinated ligand). Such mechanisms are often observed in allylic substitution reactions, even for nucleophiles derived from weakly acidic pro-nucleophiles.^{57, 58} Another mechanistic scenario is the lithium of the pro-nucleophile binds to the amino groups of the ligand during the transmetalation, causing the transmetalation to occur with high diastereoselectivity. Finally, we cannot rule out any coordination of the pyridyl nitrogen to Pd to facilitate the deprotonation of the pro-nucleophile.

Scheme 8 Plausible Mechanism



Conclusions

In summary, azaarylmethyl amines are important building blocks in medicinal chemistry. We have developed the first enantioselective (2-naphthyl)methylation of azaarylmethyl amine pronucleophiles. The benzylic substitution could be easily performed using a Pd/Mandyphos system. The potential utility has been demonstrated by the scope and scalability of the reaction. Mechanistic studies point to the importance of binding of the Li^+ to the azaaryl moiety in the deprotonation step. We envision that this method could provide a complementary strategy for the preparation of enantioenriched (2-naphthyl)methyl azaarylmethyl amines.

Author Contributions

SC performed the optimization of the reaction. The substrate scope and product characterization were performed by SC with help from JT and DX. The first draft was written by SC and all authors contributed to revising the draft. The research was directed by PJW, JM and YS.

Conflicts of interest

The authors declare no competing financial interest

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References

- P. Bhutani, G. Joshi, N. Raja, N. Bachhav, P. K. Rajanna, H. Bhutani, A. T. Paul and R. Kumar, U.S. FDA Approved Drugs from 2015–June 2020: A Perspective, *J. Med. Chem.*, 2021, **64**, 2339-2381.
- E. Vitaku, D. T. Smith and J. T. Njardarson, Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals, *J. Med. Chem.*, 2014, **57**, 10257-10274.
- P. M. Wright, I. B. Seiple and A. G. Myers, The evolving role of chemical synthesis in antibacterial drug discovery, *Angew. Chem. Int. Ed.*, 2014, **53**, 8840-8869.
- B. Linclau, Z. Wang, B. Jeffries, J. Graton, R. J. Carbajo, D. Sinnaeve, J. Y. Le Questel, J. S. Scott and E. Chiarparin, Relating Conformational Equilibria to Conformer-Specific Lipophilicities: New Opportunities in Drug Discovery, *Angew. Chem. Int. Ed.*, 2021, DOI: 10.1002/anie.202114862, e202114862.
- S. Agnello, M. Brand, M. F. Chellat, S. Gazzola and R. Riedl, A Structural View on Medicinal Chemistry Strategies against Drug Resistance, *Angew. Chem. Int. Ed.*, 2019, **58**, 3300-3345.
- D. J. Foley, A. Nelson and S. P. Marsden, Evaluating New Chemistry to Drive Molecular Discovery: Fit for Purpose?, *Angew. Chem. Int. Ed.*, 2016, **55**, 13650-13657.
- Effects of SCH 59228, an orally bioavailable farnesyl protein transferase inhibitor, on the growth of oncogene-transformed fibroblasts and a human colon carcinoma xenograft in nude mice, *Cancer Chemother. Pharmacol.*, 1998, **43**.
- H. Anagnostopoulos, R. R. Bartlett, U. Elben and P. Stoll, Synthesis of basic substituted pyridines: a new class of antiasthmatic-antiallergic agents, *Eur. J. Med. Chem.*, 1989, **24**, 227-232.
- V. Summa, A. Petrocchi, V. G. Matassa, C. Gardelli, E. Muraglia, M. Rowley, O. G. Paz, R. Laufer, E. Monteagudo and P. Pace, 4,5-Dihydroxypyrimidine Carboxamides and N-Alkyl-5-hydroxypyrimidinone Carboxamides Are Potent, Selective HIV Integrase Inhibitors with Good Pharmacokinetic Profiles in Preclinical Species, *J. Med. Chem.*, 2006, **49**, 6646-6649.
- D. C. Blakemore, L. Castro, I. Churcher, D. C. Rees, A. W. Thomas, D. M. Wilson and A. Wood, Organic synthesis provides opportunities to transform drug discovery, *Nat. Chem.*, 2018, **10**, 383-394.
- C. Chen, P. M. Pfluger, P. Chen and G. Liu, Palladium(II)-Catalyzed Enantioselective Aminotrifluoromethoxylation of Unactivated Alkenes using CsOCF_3 as a Trifluoromethoxide Source, *Angew. Chem. Int. Ed.*, 2019, **58**, 2392-2396.
- C. Hou, P. Chen and G. Liu, Enantioselective Palladium(II)-Catalyzed Oxidative Aminofluorination of Unactivated Alkenes with $\text{Et}_4\text{NF} \cdot 3\text{HF}$ as a Fluoride Source, *Angew. Chem. Int. Ed.*, 2020, **59**, 2735-2739.
- J. He, Y. Xue, B. Han, C. Zhang, Y. Wang and S. Zhu, Nickel-Catalyzed Asymmetric Reductive 1,2-Carboamination of Unactivated Alkenes, *Angew. Chem. Int. Ed.*, 2020, **59**, 2328-2332.
- F. Chen, Y. Zhang, L. Yu and S. Zhu, Enantioselective NiH/Pmrox-Catalyzed 1,2-Reduction of α,β -Unsaturated Ketones, *Angew. Chem. Int. Ed.*, 2017, **56**, 2022-2025.
- H. Kwong, H. Yeung, C. Yeung, W. Lee, C. Lee and W. Wong, Chiral pyridine-containing ligands in asymmetric catalysis, *Coord. Chem. Rev.*, 2007, **251**, 2188-2222.
- G. Chelucci, Metal-complexes of optically active amino- and imino-based pyridine ligands in asymmetric catalysis, *Coord. Chem. Rev.*, 2013, **257**, 1887-1932.
- D. M. Spero and S. R. Kapadia, A Novel Method for the Asymmetric Synthesis of α,α -Disubstituted Alkylamines via Grignard Additions to Ketimines, *J. Org. Chem.*, 1997, **62**, 5537-5541.

- 18 J. Bian, D. Blakemore, J. S. Warmus, J. Sun, M. Corbett, C. R. Rose and B. M. Bechle, Diastereoselective Synthesis of β -Heteroaryl syn- α -Methyl- β -Amino Acid Derivatives via a Double Chiral Auxiliary Approach, *Org. Lett.*, 2013, **15**, 562-565.
- 19 M. Xiao, X. Yue, R. Xu, W. Tang, D. Xue, C. Li, M. Lei, J. Xiao and C. Wang, Transition-Metal-Free Hydrogen Autotransfer: Diastereoselective N-Alkylation of Amines with Racemic Alcohols, *Angew. Chem. Int. Ed.*, 2019, **58**, 10528-10536.
- 20 F. Chen, D. He, L. Chen, X. Chang, D. Z. Wang, C. Xu and X. Xing, Chirality-Economy Catalysis: Asymmetric Transfer Hydrogenation of Ketones by Ru-Catalysts of Minimal Stereogenicity, *ACS Catalysis*, 2019, **9**, 5562-5566.
- 21 A. Schumacher, M. Bernasconi and A. Pfaltz, Chiral N-heterocyclic carbene/pyridine ligands for the iridium-catalyzed asymmetric hydrogenation of olefins, *Angew. Chem. Int. Ed.*, 2013, **52**, 7422-7425.
- 22 X. Liu, Y. Liu, G. Chai, B. Qiao, X. Zhao and Z. Jiang, Organocatalytic Enantioselective Addition of α -Aminoalkyl Radicals to Isoquinolines, *Org. Lett.*, 2018, **20**, 6298-6301.
- 23 R. S. J. Proctor, H. J. Davis and R. J. Phipps, Catalytic enantioselective Minisci-type addition to heteroarenes, *Science*, 2018, **360**, 419.
- 24 B. M. Trost and D. A. Thaisrivongs, Palladium-Catalyzed Regio-, Diastereo-, and Enantioselective Benzylic Allylation of 2-Substituted Pyridines, *J. Am. Chem. Soc.*, 2009, **131**, 12056-12057.
- 25 B. M. Trost and D. A. Thaisrivongs, Strategy for Employing Unstabilized Nucleophiles in Palladium-Catalyzed Asymmetric Allylic Alkylations, *J. Am. Chem. Soc.*, 2008, **130**, 14092-14093.
- 26 B. M. Trost, S. M. Spohr, A. B. Rolka and C. A. Kalnms, Desymmetrization of Phosphinic Acids via Pd-Catalyzed Asymmetric Allylic Alkylation: Rapid Access to P-Chiral Phosphinates, *J. Am. Chem. Soc.*, 2019, **141**, 14098-14103.
- 27 X. J. Liu and S. L. You, Enantioselective Iridium-Catalyzed Allylic Substitution with 2-Methylpyridines, *Angew. Chem. Int. Ed.*, 2017, **56**, 4002-4005.
- 28 R. Murakami, K. Sano, T. Iwai, T. Taniguchi, K. Monde and M. Sawamura, Palladium-Catalyzed Asymmetric C(sp³)-H Allylation of 2-Alkylpyridines, *Angew. Chem. Int. Ed.*, 2018, **57**, 9465-9469.
- 29 T. B. Wright and P. A. Evans, Catalytic Enantioselective Alkylation of Prochiral Enolates, *Chem. Rev.*, 2021, **121**, 9196-9242.
- 30 O. Pamies, J. Margalef, S. Canellas, J. James, E. Judge, P. J. Guiry, C. Moberg, J. E. Backvall, A. Pfaltz, M. A. Pericas and M. Dieguez, Recent Advances in Enantioselective Pd-Catalyzed Allylic Substitution: From Design to Applications, *Chem. Rev.*, 2021, **121**, 4373-4505.
- 31 Y. Sempere and E. M. Carreira, Trimethyl Orthoacetate and Ethylene Glycol Mono-Vinyl Ether as Enolate Surrogates in Enantioselective Iridium-Catalyzed Allylation, *Angew. Chem. Int. Ed.*, 2018, **57**, 7654-7658.
- 32 B. S. Zeng, X. Yu, P. W. Siu and K. A. Scheidt, Catalytic enantioselective synthesis of 2-aryl-chromenes, *Chem. Sci.*, 2014, **5**, 2277-2281.
- 33 J. Xu, O. P. Bercher and M. P. Watson, Overcoming the Naphthyl Requirement in Stereospecific Cross-Couplings to Form Quaternary Stereocenters, *J. Am. Chem. Soc.*, 2021, **143**, 8608-8613.
- 34 M. R. Harris, L. E. Hanna, M. A. Greene, C. E. Moore and E. R. Jarvo, Retention or Inversion in Stereospecific Nickel-Catalyzed Cross-Coupling of Benzylic Carbamates with Arylboronic Esters: Control of Absolute Stereochemistry with an Achiral Catalyst, *J. Am. Chem. Soc.*, 2013, **135**, 3303-3306.
- 35 F. Zhu, Q. W. Shen, W. Z. Wang, Z. L. Wu, T. Cai, W. Wen and Q. X. Guo, Direct Catalytic Asymmetric α -Allylic Alkylation of Aza-aryl Methylamines by Chiral-Aldehyde-Involved Ternary Catalysis System, *Org. Lett.*, 2021, **23**, 1463-1467.
- 36 J. Le Bras and J. Muzart, Production of Csp³-Csp³ Bonds through Palladium-Catalyzed Tsuji-Trost-Type Reactions of (Hetero)Benzylic Substrates, *Eur. J. Org. Chem.*, 2016, **2016**, 2565-2593.
- 37 K. J. Schwarz, C. Yang, J. W. B. Fyfe and T. N. Snaddon, Enantioselective α -Benzoylation of Acyclic Esters Using π -Extended Electrophiles, *Angew. Chem. Int. Ed.*, 2018, **57**, 12102-12105.
- 38 S. Tabuchi, K. Hirano and M. Miura, Palladium-Catalyzed Asymmetric Benzylic Alkylation of Active Methylene Compounds with α -Naphthylbenzyl Carbonates and Pivalates, *Angew. Chem. Int. Ed.*, 2016, **55**, 6973-6977.
- 39 H. M. Wisniewska, E. C. Swift and E. R. Jarvo, Functional-Group-Tolerant, Nickel-Catalyzed Cross-Coupling Reaction for Enantioselective Construction of Tertiary Methyl-Bearing Stereocenters, *J. Am. Chem. Soc.*, 2013, **135**, 9083-9090.
- 40 Q. Zhou, H. D. Srinivas, S. Dasgupta and M. P. Watson, Nickel-Catalyzed Cross-Couplings of Benzylic Pivalates with Arylboroxines: Stereospecific Formation of Diarylalkanes and Triarylmethanes, *J. Am. Chem. Soc.*, 2013, **135**, 3307-3310.
- 41 K. J. Schwarz, C. Yang, J. W. B. Fyfe and T. N. Snaddon, Enantioselective α -Benzoylation of Acyclic Esters Using π -Extended Electrophiles, *Angew. Chem. Int. Ed.*, 2018, **57**, 12102-12105.
- 42 M. G. J. Doyle, A. L. Gabbey, W. McNutt and R. J. Lundgren, Enantioselective Tertiary Electrophile (Hetero)Benzoylation: Pd-Catalyzed Substitution of Isoprene Monoxide with Arylacetates, *Angew. Chem. Int. Ed.*, 2021, **60**, 26495-26499.
- 43 S. R. Waetzig and J. A. Tunge, Regio- and Diastereoselective Decarboxylative Coupling of Heteroaromatic Alkanes, *J. Am. Chem. Soc.*, 2007, **129**, 4138-4139.
- 44 P. J. Moon, Z. Wei and R. J. Lundgren, Direct Catalytic Enantioselective Benzoylation from Aryl Acetic Acids, *J. Am. Chem. Soc.*, 2018, **140**, 17418-17422.
- 45 R. R. Fraser, T. S. Mansour and S. Savard, Acidity measurements on pyridines in tetrahydrofuran using lithiated silylamines, *J. Org. Chem.*, 1985, **50**, 3232-3234.
- 46 F. G. Bordwell, Equilibrium acidities in dimethyl sulfoxide solution, *Acc. Chem. Res.*, 1988, **21**, 456-463.
- 47 J. Mao, J. Zhang, H. Jiang, A. Bellomo, M. Zhang, Z. Gao, S. D. Dreher and P. J. Walsh, Palladium-Catalyzed Asymmetric Allylic Alkylations with Toluene Derivatives as Pronucleophiles, *Angew. Chem. Int. Ed.*, 2016, **55**, 2526-2530.
- 48 B. S. Kim, J. Jimenez, F. Gao and P. J. Walsh, Palladium-Catalyzed Benzylic C-H Arylation of Azaarylmethylamines, *Org. Lett.*, 2015, **17**, 5788-5791.
- 49 S. C. Sha, H. Jiang, J. Mao, A. Bellomo, S. A. Jeong and P. J. Walsh, Nickel-Catalyzed Allylic Alkylation with Diarylmethane Pronucleophiles: Reaction Development and Mechanistic Insights, *Angew. Chem. Int. Ed.*, 2016, **55**, 1070-1074.
- 50 S. C. Sha, J. Zhang, P. J. Carroll and P. J. Walsh, Raising the pKa limit of "soft" nucleophiles in palladium-catalyzed allylic substitutions: application of diarylmethane pronucleophiles, *J. Am. Chem. Soc.*, 2013, **135**, 17602-17609.
- 51 F. L. Zhu, Y. Zou, D. Y. Zhang, Y. H. Wang, X. H. Hu, S. Chen, J. Xu and X. P. Hu, Enantioselective copper-catalyzed decarboxylative propargylic alkylation of propargyl β -ketoesters with a chiral ketimine P,N,N-ligand, *Angew. Chem. Int. Ed.*, 2014, **53**, 1410-1414.
- 52 K. J. Schwarz, J. L. Amos, J. C. Klein, D. T. Do and T. N. Snaddon, Uniting C1-Ammonium Enolates and Transition Metal Electrophiles via Cooperative Catalysis: The Direct Asymmetric α -Allylation of Aryl Acetic Acid Esters, *J. Am. Chem. Soc.*, 2016, **138**, 5214-5217.

Journal Name

ARTICLE

53 X. Cao, S. C. Sha, M. Li, B. S. Kim, C. Morgan, R. Huang, X. Yang and P. J. Walsh, Nickel-Catalyzed Arylation of Heteroaryl-containing Diarylmethanes: Exceptional Reactivity of the Ni(NIXANTPHOS)-based Catalyst, *Chem. Sci.*, 2016, **7**, 611-618.

54 R. D. Taylor, M. MacCoss and A. D. Lawson, Rings in drugs, *J. Med. Chem.*, 2014, **57**, 5845-5859.

55 T. T. Talele, The "Cyclopropyl Fragment" is a Versatile Player that Frequently Appears in Preclinical/Clinical Drug Molecules, *J. Med. Chem.*, 2016, **59**, 8712-8756.

56 R. Kuwano, M. Yokogi, K. Sakai, S. Masaoka, T. Miura and S. Won, Room-Temperature Benzylic Alkylation of Benzylic Carbonates: Improvement of Palladium Catalyst and Mechanistic Study, *Org. Process Res. Dev.*, 2019, **23**, 1568-1579.

57 S.-C. Sha, J. Zhang, P. J. Carroll and P. J. Walsh, Raising the pKa Limit of "Soft" Nucleophiles in Palladium-Catalyzed Allylic Substitutions: Application of Diarylmethane Pronucleophiles, *J. Am. Chem. Soc.*, 2013, **135**, 17602-17609.

58 S. C. Sha, H. Jiang, J. Mao, A. Bellomo, S. A. Jeong and P. J. Walsh, Nickel-Catalyzed Allylic Alkylation with Diarylmethane Pronucleophiles: Reaction Development and Mechanistic Insights, *Angew. Chem. Int. Ed.*, 2016, **55**, 1070-1074.