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Rhodium-Catalyzed Asymmetric Hydroamination of Allyl Amines

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Abstract

A Rh-catalyzed enantioselective hydroamination of allylamines using a chiral BIPHEP-type ligand is reported. Enantioenriched 1,2-diamines are formed in good yields and with excellent enantioselectivities. A diverse array of nucleophiles and amine directing groups are demonstrated, including deprotectable motifs. Finally, the methodology was demonstrated toward the rapid synthesis of 2-methyl-moclobemide.

Efficient strategies toward the synthesis of chiral amines are highly desirable as these frameworks are present in an estimated 45% of pharmaceutical drug candidates.¹ The asymmetric hydroamination of olefins offers an elegant, 100% atom-economical approach to this important moiety in a single step from easily accessible starting materials; however, a direct, intermolecular variant remains an important unsolved challenge.² Significant progress has been made in the field since Togni's seminal report on the asymmetric [Ir]-catalyzed intermolecular hydroamination of norbornene.³ Namely, the asymmetric hydroamination of norbornadienes, styrenes, and dienes have been reported to occur with good to high enantioselectivities.⁴ In turn, unactivated olefins have also been shown to undergo direct asymmetric hydroamination, however, only modest enantioselectivities have been observed (up to 89:11 er).^{5,6} Recently, the copper-catalyzed hydroamination of alkenes using electrophilic amines and silanes has been reported to occur with excellent enantioselectivities.^{7–9}

Chiral 1,2-diamines represent an important subclass of chiral amines that are not only prevalent in pharmaceuticals (Figure 1) but also represent a class of privileged ligands for asymmetric catalysis.¹⁰ These amines, often derived from ethylene or propylene diamine, have important effects on the human body.¹¹ Interestingly, the minor change from a 1,2-ethylene diamine to a 1,2-propylene diamine has been correlated to stark increased in

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental details, characterization data, and crystallographic data (PDF, mnova, cif).

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potency for some drugs. This is referred to as the “magic methyl effect”.¹² For instance, the methylation of PLD2 inhibitor I to II afforded a drug molecule 590 times more potent.¹² An asymmetric synthesis of 1,2-diamines, via an organocatalyzed hydroamination, has been reported by Beauchemin, however, variable enantioselectivities were observed due to racemization of the first generation catalyst (Scheme 1).¹³

As part of our ongoing research program we have reported the hydroamination of allyl imines and amines to form 1,2-diamines in excellent yields, with high regio-, and diastereoselectivities.^{14,15} While the initial reports demonstrated promising reactivity, we recognized that true synthetic utility for this transformation would require the development of an enantioselective variant and therefore sought to develop a straightforward and efficient synthesis of chiral 1,2-diamines.

To achieve this goal, we utilized high throughput experimentation (HTE) with the Merck Catalysis Laboratory and screened 288 chiral bidentate ligands combined with Rh(nbd)₂BF₄ for the hydroamination of allyl amine 1a with morpholine (Table 1). Of these ligands, only 9 formed >1% of the desired product, despite the library spanning all common available classes of chiral bidentate ligands.¹⁶ A variety of reactivity and selectivity was observed from the newly formed Rh-ligand complexes. The results indicated that the reaction is sensitive to steric bulk at the phosphorous center (see L1 to L3). Most poignant, however, was the difference in reactivity between L6 and L7. Simply modifying the phosphine substituents from p-tolyl groups to 2-furyl groups led to a dramatic increase in reactivity. This is likely due to the furyl substituents rendering the phosphorous centers more electrophilic, thereby enhancing the rhodium center's ability to coordinate to the olefin via π -backbonding and facilitating aminometallation.¹⁷ Consistent with this hypothesis, only a small excess of nucleophile (1.2 equiv) is required for high conversion with L6 relative to our initial hydroamination conditions that used DPEphos and required 1.5–5.0 equivalents.^{14a} While several of the ligands showed promising results, we chose to continue our studies with the Rh complex of MeO-BIPHEP ligand L6, as it promotes the hydroamination reaction in good yields and excellent enantioselectivity.

Next, we undertook optimization of the reaction conditions and discovered that increasing the concentration 10 fold and changing from 10 to 3 mol % catalyst allowed for better reactivity and modestly reduced enantioselectivity to 94.2:5.8 er (Table S2, entry 2). Solvent, concentration, and catalyst loading screens revealed that DME at a decreased concentration and with 5 mol% catalyst was superior. Under these optimized conditions 2a was afforded in 92% yield and 96.6:3.4 er (Table S2, entry 8).¹⁸ Notably, the synthesis of 2a was performed on a 2.0 mmol scale with 2.5 mol % [Rh], affording 75% yield of the desired product with no loss in enantioselectivity.

With the optimized conditions in hand, we explored the scope of the asymmetric hydroamination reaction. A series of electronically diverse aryl and heteroaryl rings can be incorporated in the substrate with minimal impact on enantioselectivity (2a-2i, Table 2). The reaction is tolerant of a variety of functionalities, including aryl ethers (2a, 2e, and 2i), a tertiary amine (2b), a trifluoromethyl group (2c), an aryl bromide (2d), and an ester (2f). A single ortho-substituent on the aryl ring had little effect on the reactivity, as 2e is formed in

82% yield and 97.2:2.8 er. Impressively, the highly hindered 2,4,6-trimethoxy benzyl substituent is also tolerated, though it requires an increased reaction concentration (0.5 M) to reach completion (2i). Additionally, hydroamination products containing modestly Lewis basic heterocycles were formed in very good yields (2g, 2h). No products were observed when the more Lewis basic 2-pyridyl substrate was subjected to the reaction conditions, likely due to its coordination to the catalysts. Notably, it is not necessary that the secondary amine directing group contains a π -system; for example, simple aliphatic substitution, i.e. cyclohexyl, can be employed with little impact on the yield or enantioselectivity of the desired products (2j, 2k, 2m). In fact, as can be seen in products 2j and 2k, a stereogenic center on the aliphatic directing group presents no difficulty to enantioinduction; i.e., the favored diastereomer is governed solely by catalyst control. Unfortunately, using either an α -branched amine, a primary amine, or a tertiary amine as the directing group failed to afford the desired products. As with our previous work, N-allyl imines did undergo the hydroamination reaction, however with a significant reduction in the enantioselectivity (after reduction of the corresponding imine, 2a was afforded in only 80:20 er).¹⁵

The scope of nucleophiles that are amenable to this transformation is likewise quite broad (Table 3). For example, 4-, 5-, and 6-membered secondary cyclic amines are all competent nucleophiles, providing products in excellent enantiomeric ratios (3a-3c). Unfortunately, employing azepane (not depicted) as a nucleophile, affords an unsatisfactory 25% NMR yield of the desired product with 10 mol % catalyst, likely due to its diminished nucleophilicity.¹⁹ Similarly, tetrahydroisoquinoline requires a 2-fold increase in both concentration and catalyst loading to provide good reactivity (3d). We next investigated more complex and synthetically relevant nucleophiles, beginning with substituted piperazines. The Lewis basic 1-pyrimidylpiperazine was successfully utilized as a nucleophile with similar reactivity and selectivity as was observed with piperidine (3e and 3f vs. 3c). Excitingly, 1-(2-hydroxyethyl)piperazine can be used without protection of the free hydroxyl group, showing a tolerance for primary aliphatic alcohols (3g). 1-Boc-piperazine is an excellent nucleophile and affords 3h in 88% yield and 93.4:6.6 er. This nucleophile is especially advantageous, as the Boc group can readily undergo deprotection, providing an attractive handle for subsequent derivatization of the piperazine. Acetals are also compatible with the reaction conditions, as 1,4-dioxo-8-azaspiro[4,5]decane, a known ammonia surrogate,²⁰ is an effective nucleophile, affording 3i in 69% yield with a 96.2:3.85 er. Hindered 3,5-dimethylmorpholine requires a higher reaction concentration to afford a good yield (68%) of the product, although in a slightly lower enantiomeric ratio (92.6:7.4) (3k). Both N-methylbenzylamine and dimethylamine are effective nucleophiles to form 3l and 3m in 69% yield (94.3:5.7 er) and 44% yield (88.0:12.0 er), respectively. Diethylamine fails to undergo the hydroamination reaction, implying that one substituent must be methyl in order for an acyclic amine to engage as a nucleophile in this transformation. Further, the hydroamination products were not observed with nucleophiles containing a highly Lewis basic group (3n) or strongly chelating functionality (3o). Further, we have endeavored to show that our methodology allows rapid access to the synthetically challenging 1,2-propylene diamine motif by synthesizing a C–H methylation derivative of the clinically used antidepressant Moclobemide (eq. 1). Intriguingly, 2a is decomposed completely under traditional oxidative cleavage conditions with CAN or DDQ, requiring the use of a

nonstandard method employing phenol and phosphoric acid.²¹ This concise and highly diversifiable synthesis of this pharmaceutical derivative demonstrates the power of this method to efficiently generate drug analogues which may then be tested for the “magic methyl effect.”

(1)

The asymmetric hydroamination of unactivated olefins is a highly sought-after and elusive reaction in method development and catalysis. We have discovered that MeO-BIPHEP ligand L6, in combination with Rh, promotes a hydroamination reaction of allylamines to provide the corresponding 1,2-diamines in high yields and excellent enantioselectivities. A wide variety of secondary cyclic amine nucleophiles, as well as methylbenzylamine and dimethylamine, can be utilized in this transformation. The generality of using a secondary amine as the directing group and to tolerate aryl halides and deprotectable amines, i.e. 3h and 3l, allows for great diversity in product classes accessible by this transformation. Furthermore, this reaction can be utilized to generate products that are members of a known class of biologically active molecules, and produces the desired 1,2-diamine motif in a drastically more efficient manner than is currently used. Our laboratory is currently studying the mechanism of this transformation and expanding this strategy to additional hydrofunctionalization reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Ghislieri D; Green AP; Pontini M; Willies SC; Rowles I; Frank A; Grogan G; Turner NJ Engineering an Enantioselective Amine Oxidase for the Synthesis of Pharmaceutical Building Blocks and Alkaloid Natural Products. *J. Am. Chem. Soc* 2013, 135, 10863–10869. [PubMed: 23808566]
2. Nishina N; Yamamoto Y Hydrofunctionalization Topics in Organometallic Chemistry, 2012, 115–143.
3. Dorta R; Egli P; Zürcher F; Togni A The [IrCl(Diphosphine)]₂/Fluoride System. Developing Catalytic Asymmetric Olefin Hydroamination. *J. Am. Chem. Soc* 1997, 119, 10857–10858.
4. (a) Katatsura M; Hartwig JF Palladium-Catalyzed Intermolecular Hydroamination of Vinylarenes Using Arylamines. *J. Am. Chem. Soc* 2000, 122, 9546–9547; (b) Hu A; Ogasawara M; Sakamoto T; Okada A; Nakajima K; Takahashi T; Lin W Palladium-Catalyzed Intermolecular Asymmetric Hydroamination with 4,4'-Disubstituted BINAP and SEGPHOS. *Adv. Synth. Catal* 2006, 348, 2051–2056; (c) Cooke ML; Xu K; Breit B Enantioselective Rhodium-Catalyzed Synthesis of Branched Allylic Amines by Intermolecular Hydroamination of Terminal Allenes. *Angew. Chem.*

- Int. Ed 2012, 51, 10876–10879;(d)Huang L; Arndt M; Gooßen K; Heydt H; Gooßen LJ Late Transition Metal-Catalyzed Hydroamination and Hydroamidation. Chem. Rev 2015, 115, 2596–2697; [PubMed: 25721762] (e)Adamson NJ; Hull E; Malcolmson SJ Enantioselective Intermolecular Addition of Aliphatic Amines to Acyclic Dienes with a Pd–PHOX Catalyst. J. Am. Chem. Soc 2017, 139, 7180–7183; [PubMed: 28453290] (f)Kim S; Wurm T; Brito GA; Jung W; Zbieg JR; Stivala CE; Krische MJ Hydroamination versus Allylic Amination in Iridium-Catalyzed Reactions of Allylic Acetates with Amines: 1,3-Aminoalcohols via Ester-Directed Regioselectivity. J. Am. Chem. Soc 2018, 140, 9087–9090. [PubMed: 29989803]
5. Zhang Z; Lee SD; Widenhoefer RA Intermolecular Hydroamination of Ethylene and 1-Alkenes with Cyclic Ureas Catalyzed by Achiral and Chiral Gold(I) Complexes. J. Am. Chem. Soc 2009, 131, 5372–5373. [PubMed: 19326908]
6. Reznichenko A; Nguyen HN; Hultsch KC Asymmetric Intermolecular Hydroamination of Unactivated Alkenes with Simple Amines. Angew. Chem. Int. Ed 2010, 49, 8984–8987.
7. Pirnot MT; Wang Y; Buchwald SL Copper Hydride Catalyzed Hydroamination of Alkenes and Alkynes. Angew. Chem. Int. Ed 2016, 55, 48–57.
8. (a)Rucker RP; Whittaker AM; Dang H; Lalic G Synthesis of Tertiary Alkyl Amines from Terminal Alkenes: Copper-Catalyzed Amination of Alkyl Boranes. J. Am. Chem. Soc 2012, 134, 6571–6574; [PubMed: 22469028] (b)Zhu S; Niljianskul N; Buchwald SL Enantio- and Regioselective CuH-Catalyzed Hydroamination of Alkenes. J. Am. Chem. Soc 2013, 135, 15746–15749; [PubMed: 24106781] (c)Miki Y; Hirano K; Satoh T; Miura M Copper-Catalyzed Intermolecular Regioselective Hydroamination of Styrenes with Polymethylhydrosiloxane and Hydroxylamines. Angew. Chem. Int. Ed 2013, 52, 10830–10834;(d)Yang Y; Shi SL; Niu D; Liu P Buchwald SL Catalytic asymmetric hydroamination of unactivated internal olefins to aliphatic amines. Science, 2015, 349, 62–66; [PubMed: 26138973] (e)Zhu S; Niljianskul N; Buchwald SL A direct approach to amines with remote stereocentres by enantioselective CuH-catalysed reductive relay hydroamination. Nat. Chem 2016, 8, 144–150. [PubMed: 26791897]
9. (a)Zhu S; Buchwald SL Enantioselective CuH-Catalyzed Anti-Markovnikov Hydroamination of 1,1-Disubstituted Alkenes J. Am. Chem. Soc 2014, 136, 15913–15916; [PubMed: 25339089] (b)Xi Y; Butcher TW; Zhang J; Hartwig JF Regioselective, Asymmetric Formal Hydroamination of Unactivated Internal Alkenes. Angew. Chem. Int. Ed 2016, 55, 776–780.
10. (a)Michalson ET; Szmuszkovicz J Medicinal agents incorporating the 1,2-diamine functionality. Prog. Drug Res 1989, 33, 135–149; [PubMed: 2687936] (b)Kizirian J Chiral Tertiary Diamines in Asymmetric Synthesis. Chem. Rev 2008, 108, 140–205. [PubMed: 18081351] (c)Shen P; hu L; Shao Q; Hong K; Yu J Pd(II)-Catalyzed Enantioselective C(sp³)-H Arylation of Free Carboxylic Acids. J. Am. Chem. Soc 2018, 140, 6545–6549 [PubMed: 29741883]
11. (a)Schechter LE; Smith DL; Rosenzweig-Lipson S; Sukoff SJ; Dawson LA; Marquis K; Jones D; Piesla M; Andree T; Nawoschik S; Harder JA; Womack MD Buccafusco J; Terry AV Hoebel B; Rada P; Kelly M; Abou-Gharbia M; Barrett JE Childers W Lecozone (SRA-333): A Selective Serotonin 1A Receptor Antagonist That Enhances the Stimulated Release of Glutamate and Acetylcholine in the Hippocampus and Possesses Cognitive-Enhancing Properties. J. Pharmacol. Exp. Ther 2005, 314, 1274–1289; [PubMed: 15951399] (b)Childers WE; Abou-Gharbia MA; Andree TH; Harrison BL; Ho DM; Hornby G; Hurn DM Potestio L; Rosenzweig-Lipson SJ; Schmid J; Smith DL; Sukoff SJ; Zhang G; Schechter LE Synthesis and Biological Evaluation of Benzodioxanypiperazine Derivatives as Potent Serotonin 5-HT_{1A} Antagonists: The Discovery of Lecozone. J. Med. Chem 2005, 48, 3467–3470. [PubMed: 15887953]
12. Schönherr H; Cernak T Profound Methyl Effects in Drug Discovery and a Call for New C–H Methylation Reactions. Angew. Chem. Int. Ed 2013, 52, 12256–12267.
13. MacDonald MJ; Hesp CR; Schipper DJ; Pesant M; Beauchemin AM Highly Enantioselective Intermolecular Hydroamination of Allylic Amines with Chiral Aldehydes as Tethering Catalysts. Chem. Eur. J 2013, 19, 2597–2601. [PubMed: 23307591]
14. (a)Ensign SC; Vanable EP; Kortman GD; Weir LJ; Hull KL Anti-Markovnikov Hydroamination of Homoallylic Amines. J. Am. Chem. Soc 2015, 137, 13748–13751; [PubMed: 26456593] (b)Kennemur JL; Kortman DG; Hull KL Rhodium-Catalyzed Regiodivergent Hydrothiolation of Allyl Amines and Imines. J. Am. Chem. Soc 2016, 138, 11914–11919; [PubMed: 27547858] (d)Kohler DG; Gockel SN; Kennemur JL; Waller PJ; Hull KL Palladium-catalysed anti-Markovnikov selective oxidative amination. Nat. Chem 2018, 10, 333–340. [PubMed: 29461537]

15. Ickes AR; Ensign SC; Gupta AK; Hull KL Regio- and Chemoselective Intermolecular Hydroamination of Allyl Imines for the Synthesis of 1,2-Diamines J. Am. Chem. Soc, 2014, 136, 11256–11259. [PubMed: 25050740]
16. See Supporting information page S3-S4 for details and S54-S57 for a list of commercial ligands screened.
17. Andersen NG; Keay BA 2-Furyl Phosphines as Ligands for Transition-Metal-Mediated Organic Synthesis Chem. Rev 2001, 101, 997–1030.
18. The absolute configuration of product 2a was determined crystallographically as the bis-p- τ -toluenesulfonic acid salt where using the (S)-ligand generates the (S)-product; the stereochemistry of all other products was assigned by analogy.
19. Brotzel F; Chu YC; Mayr H Nucleophilicities of Primary and Secondary Amines in Water. J. Org. Chem 2006, 72, 3679–3688.
20. (a) Shimano M; Meyers AI Asymmetric Diastereoselective Conjugate Additions of Lithium Amides to Chiral Naphthyloxazolines Leading to Novel β -Amino Acids. J. Org. Chem 1995, 60, 7445–7455; (b) Mita T; Sugawara M; Sato Y One-Pot Synthesis of α -Amino Acids through Carboxylation of Ammonium Ylides with CO₂ Followed by Alkyl Migration. J. Org. Chem 2016, 81, 5236–5243. [PubMed: 27223669]
21. Field GF; Zally WJ; Sternbach LH; Blount JF Synthesis of α -Dehydrobiotin. J. Org. Chem 1976, 41, 3853–3857

Figure 1.
1,2-Diamines in biologically active compounds

a. Asymmetric organocatalyzed hydroamination of allyl amines

b. **This work:** Rh-catalyzed asymmetric hydroamination of allyl amines

Scheme 1.
Hydroamination to afford 1,2-diamines

Table 1.

Initial ligand screens

1a 1.0 equiv + **1.2 equiv**

10 mol % [Rh(nbd)₂]₂BF₄
 10 mol % **Ligand**
 dioxane (0.1 M), 60 °C, 16 h

2a

entry	ligand	yield ^a	e.r. ^a
1	L1	< 1%	n.d.
2	L2	33%	87.5:12.5
3	L3	52%	12.5:87.5
4	L4	11%	0.5:99.5
5	L5	52%	99.0:1.0
6	L6	63%	99.0:1.0
7	L7	14%	99.5:0.5
8	L8	22%	47.0:53.0
9	L9	32%	63.5:36.5
10	L10	22%	0.5:99.5

L1: (*R,R*), R¹ = *t*-Bu

L2: (*R,R*), R¹ = 2-Me-Ph

L3: (*S,S*), R¹ = 3,5-diMe-Ph

L4

L5

L6: R¹ = 2-Furyl

L7: R¹ = 4-Me-Ph

L8

L9

L10

Table 2.

Directing group scope

^aAllyl amine (0.20 mmol), nucleophile (0.24 mmol), [Rh(cod)₂]₂BF₄ (0.010 mmol), (*R*)-**L6** (0.010 mmol), and DME (0.25 M) at 60 °C for 16 h. Isolated yields determined by the average of duplicate runs; Enantiomeric ratio determined by HPLC of the purified product. ^b (*S*)-**L6**. ^c DME (0.50 M). ^d Diastereomeric ratio determined by ¹H NMR of the crude reaction mixture. ^e ¹H NMR yield determined by comparison to an internal standard.

Table 3.

Nucleophile scope

^{a-c} See Table 3. ^d ¹H NMR yield determined by comparison to an internal standard. ^e 10 mol % catalyst. ^f 4.8 equiv. nucleophile. ^g DME (1.0 M). ^h 0.38M.

$\text{R}^1\text{-N-CH=CH}_2 + \text{R}^2\text{-N(R}^3\text{)-H}$		$\xrightarrow[\text{DME (0.25 M), 60 }^\circ\text{C, 16 h}]{\text{5 mol \% [Rh(cod)}_2\text{]BF}_4, \text{ 5 mol \% L6}}$	$\text{R}^1\text{-N-CH}_2\text{-CH(R}^2\text{)-N(R}^3\text{)-H}$
1.0 equiv	1.2 equiv		3a-3o
 3a , 85% 94.8:5.2 ^b	 3b , 84% 97.7:2.3	 3c , 64% 95.8:4.2 ^b	
 3d , 74% 96.9:3.1 ^{c,e}	 3e , 74% 97.3:2.7 ^b	 3f , 47% 92.6:7.4 ^b	
 3g , 86% 96.7:3.3 ^f	 3h , 88% 93.4:6.6 ^e	 3i , 69% 96.2:3.8 ^{b,c}	
 3j , 41% 96.2:3.8 ^{b,c}	 3k , 68% 92.6:7.4 ^{b,c}	 3l , 69% 94.3:5.7 ^{b,e,f,g}	
 3m , 44% 88.0:12.0 ^{b,e,f,h}	 3n , NR ^d	 3o , <5% ^d	