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Enantioselective Synthesis of *anti*-1,2-Diamines by Cu-Catalyzed Reductive Couplings of Azadienes with Aldimines and Ketimines

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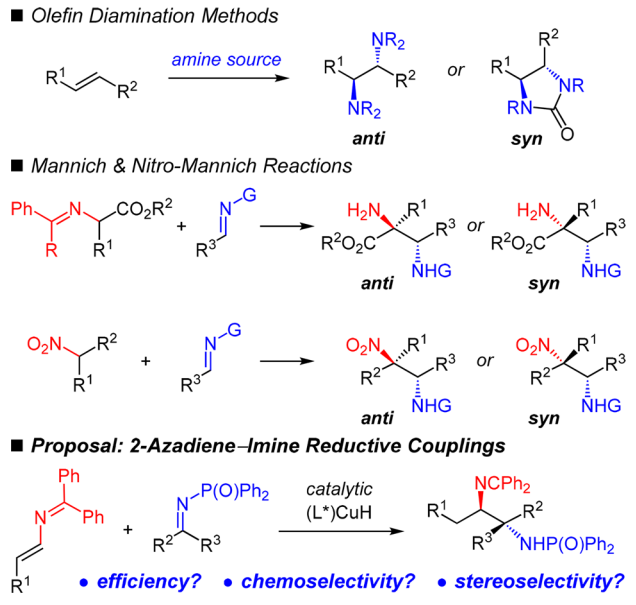
Supporting Information

ABSTRACT: Here we report highly efficient and chemoselective azadiene−imine reductive couplings catalyzed by (Ph-BPE)Cu−H that afford *anti*-1,2-diamines. In all cases, reactions take place with either aldimine or ketimine electrophiles to deliver a single diastereomer of product in >95:5 er. The products' diamines are easily differentiable, facilitating downstream synthesis.

The catalytic enantioselective preparation of vicinal diamines is an important goal in synthetic chemistry owing to the large number of pharmaceuticals, natural products, and chiral ligands that contain this motif.[1] Although several approaches to this moiety have been reported by a number of researchers, significant shortcomings in scope or the ability to differentiate the products' two amino groups constrain their utility (Scheme 1). One major strategy has utilized intermolecular olefin diamination[2] to afford either the *anti*- or *syn*-1,2-diamines.[3] In nearly all such cases, the two introduced amino groups have identical substituents, making their differentiation challenging to achieve.[4] Another strategy has employed N-substituted enolates or nitroalkanes in Mannich-type reactions;[5−7] either diastereomer may be selectively formed. However, in the former case, the requirement of an electron withdrawing group reduces the scope of diamines that may be prepared. In the latter, nitro group reduction is needed to secure the diamine.[8] In both cases, when tetrasubstituted amine-containing stereogenic centers are formed, one of that center's other substituents has been limited to a carbonyl-like group.

Scheme 1. Catalytic Enantioselective Methods for Preparing Vicinal Diamines and Proposed Strategy



To address these limitations, we sought to develop a method that would unite two N-containing reagents via catalytic enantioselective C−C bond formation such that (1) a greater diversity of 1,2-diamines, including those with N-containing tetrasubstituted stereogenic centers, might be garnered; (2) the nitrogen groups of the products would be easily differentiated in order to assist in subsequent derivatizations; and (3) either free amine could be obtained without the need for harsh reducing conditions. We envisioned that the reductive coupling of 2-azadienes[9] and suitably activated imines could allow us to realize this goal (Scheme 1). However, catalytic enantioselective reductive couplings with imines are rare.[10,11] Successful implementation of our proposed strategy would require high catalyst efficiency and control over diastereo-, enantio-, and chemoselectivity for the desired C−C bond formation (versus imine reduction[12]).

Within the last several years, enantioselective Cu-catalyzed reductive couplings[13,14] of unsaturated hydrocarbons with various C-electrophiles has rapidly emerged as an effective way for preparing myriad chemical motifs, often comprised of vicinal stereogenic centers. Vinylarenes,[10c,d,15] vinylboronic esters,[16] allenes,[11e,17] and conjugated enynes[18] and dienes[15g,18] have comprised the substrates for these processes, yet none has established vicinal heteroatom-substituted stereogenic centers. Our recent disclosure of the Cu-catalyzed reductive coupling of 2-azadienes and ketones shows the promise these reagents hold for achieving such a goal.[9] In this work, we demonstrate that 2-azadienes participate in chemoselective Cu-catalyzed reductive couplings with N-diphenylphosphinoyl (Dpp) imines. Both aldimines and ketimines react to furnish *anti*-1,2-diamines[19] with vicinal stereogenic centers, in most cases as a single stereoisomer. The two N-groups of the products, one an imine and the other a phosphinamide, are readily discriminated, enabling their subsequent divergent elaboration.

We initially explored addition of terminal 2-azadiene **1a** to Dpp-aldimine **2a** (Table 1). Optimal conditions employ 3.0 equiv of azadiene, DMMS as the reducing agent, *t*-BuOH as additive, a Cu-based catalyst with (*S*,*S*)-Ph-BPE as the ligand,

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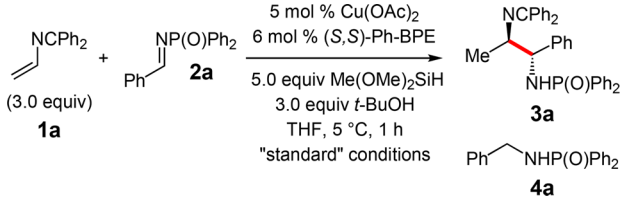
Table 1. Impact of Reaction Conditions in Azadiene–Imine Reductive Couplings[a]



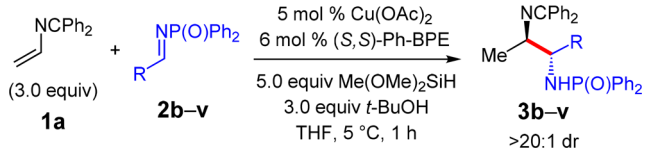
entry	variation from the entry "standard" conditions	3a:4a[b]	yield of 3a (%)[c]	dr[b]	er[d]
1	none	5:1	82	>20:1	>99:1
2	Ts, Boc et al. instead of $P(O)Ph_2$	–	–	–	–
3	22 °C	2:1	63	>20:1	>99:1
4	no *t*-BuOH	0.8:1	14	>20:1	>99:1
5	MeOH instead of *t*-BuOH	1.5:1	50	>20:1	>99:1
6	*i*-Pr-BPE instead of Ph-BPE	–	<5	–	–
7	*i*-Pr-DuPHOS instead of Ph-BPE	0.9:1	40	10:1	99:1
8	QuinoxP instead of Ph-BPE	8:1	59/16[e]	4:1	99:1

[a]Reaction under N_2 with 0.1 mmol imine **2a**. [b]Determined by 400 MHz ^{1}H NMR spectroscopy of the unpurified mixture. [c]Isolated yield of purified **3a**. [d]Determined by HPLC analysis of purified **3a** major diastereomer. [e]Yield of the major/minor diastereomer of **3a**.

and 5 °C (ice bath) reaction temperature (entry 1). After 1 h under these conditions, the desired diamine **3a** can be obtained in 82% yield, solely as the *anti*-diastereomer and as a single enantiomer. Accompanying **3a** is ca. 15% reduction product **4a**. Utilizing imine activating groups other than Dpp (e.g., Ts, Boc, etc.) results in <2% conversion to **3a** (entry 2).[10d,12] Conducting the reaction at 22 °C results in poorer chemoselectivity, delivering more of the unwanted **4a**; however, stereoselectivity remains unaffected (entry 3). Omitting *t*-BuOH not only lowers catalyst efficiency but also adversely affects chemoselectivity (entry 4), similar to observations made by the Buchwald lab in styrene–imine couplings.[10d] The identity of the alcohol additive is also critical for the selective formation of **3a** (entry 5). Although an *i*-Pr-BPE–Cu complex fails to furnish any product (entry 6), switching to *i*-Pr-DuPHOS generates **3a** in 40% yield, 10:1 dr, and 99:1 er but accompanied by a substantial quantity of **4a** (entry 7). A QuinoxP-derived catalyst, although highly selective for C–C bond formation over imine reduction (8:1), generates **3a** in only 4:1 dr (entry 8).[20]

Several aldimines undergo coupling with azadiene **1a**, leading to *anti*-diamines **3** as a single diastereomer (Table 2). In most cases, only a single enantiomer of product is generated. A variety of aryl-substituted imines participate in the reaction with the more electron rich substrates affording the highest yields (64–93%, entries 1–5, 13, 15). Halogen substituents are tolerated with diamines **3g–i** and **3o** isolated in 55–73% yield (entries 6–8, 14). More electron poor imines also yield the desired diamines **3j–l** (entries 9–11) but in somewhat diminished yields (41–59%). The observed trend is due to increasingly competitive imine reduction as the imine partner becomes more electron deficient;[21] however, boronic ester **3m** is isolated in 75% yield as a single stereoisomer (entry 12). Notably, more sterically hindered aldimines do not affect reaction efficiency: *o*-tolyl **3p** is furnished in 89% yield (entry 15). Heteroaryl aldimines can be coupled efficiently with the

Table 2. Aldimine Scope in Couplings with Azadiene 1a



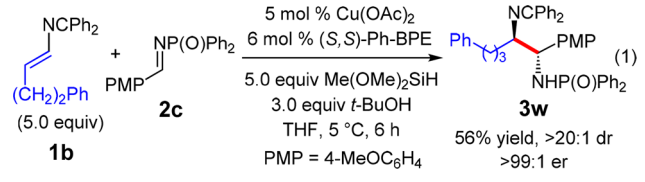
entry	product, R	yield (%)[b]	er[c]
1	**3b**, 4-$Me_2NC_6H_4$	96	>99:1
2	**3c**, 4-$MeOC_6H_4$	89	>99:1
3	**3d**, 4-$F_2HCOC_6H_4$	64	>99:1
4	**3e**, 4-$MeSC_6H_4$	82	>99:1
5	**3f**, 4-(*N*-pyrazolyl)C_6H_4	84	>99:1
6	**3g**, 4-FC_6H_4	73	>99:1
7	**3h**, 4-ClC_6H_4	62	>99:1
8	**3i**, 4-BrC_6H_4	64	>99:1
9	**3j**, 4-$MeO_2CC_6H_4$	59	>99:1
10	**3k**, 4-$F_3CC_6H_4$	44	>99:1
11[d]	**3l**, 4-NCC_6H_4	41	>99:1
12[e]	**3m**, 4-(pin)BC_6H_4	75	>99:1
13	**3n**, 2-naphthyl	85	>99:1
14	**3o**, 3-BrC_6H_4	55	>99:1
15	**3p**, 2-MeC_6H_4	89	>99:1
16	**3q**, 3-furyl	93	>99:1
17	**3r**, 3-thiophenyl	83	>99:1
18	**3s**, 3-indolyl(NMe)	94	98.5:1:5
19	**3t**, C(Me)CHPh	71	>99:1
20[f]	**3u**, CHCHPh	61	>99:1
21	**3v**, CH_2CH_2Ph	52	>99:1

[a]Reaction under N_2 with 0.2 mmol imine **2**. Dr measured by 400 MHz ^{1}H NMR spectroscopy of the unpurified mixture. [b]Isolated yield of purified **3**. [c]Determined by HPLC analysis of purified **3**. [d]5.0 equiv **1a**. [e]4.0 equiv **1a**. [f]Formed as a 4:1 mixture of **3u**:**3v**; yield of isolated **3u**.

terminal azadiene as well to generate diamines **3q–s** in 83–94% yield (entries 16–18).

Unsaturated imines also undergo efficient coupling with azadiene **1a** (entries 19 and 20). Allylic amine **3t**, bearing a trisubstituted olefin, is formed in 71% yield. The less hindered cinnamyl **3u** is isolated in 61% yield but the reductive coupling also affords ca. 15% of saturated diamine. An alkyl-substituted imine leads to 52% yield of saturated diamine **3v** in >99:1 er (entry 21). An alkynyl aldimine failed to deliver the desired diamine product.

We also examined the coupling of 4-substituted 2-azadienes with aldimines to deliver diamines comprised of α-alkyl groups other than methyl. As typified in eq 1, the added steric



hindrance of azadiene **1b** leads to slower Cu–H insertion and a more competitive reduction, which adversely affects the diamine yield. An electron rich aldimine, such as **2c**, and an extended reaction time (6 h) are required to obtain good yield of **3w**. Increasing to 5.0 equiv of azadiene improves the reaction as well with the product then isolated in 56% yield (versus 42% with 3.0 equiv **1b**), >20:1 dr, and >99:1 er.

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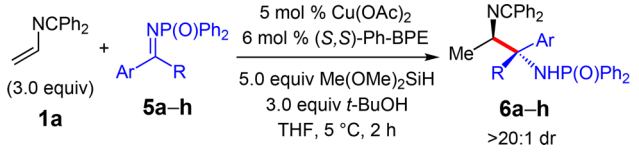
We next sought to test whether azadiene couplings with ketimines would enable the synthesis of 1,2-diamines wherein one stereogenic center is fully substituted. Reactions that form such motifs wherein both amines are bound to stereogenic centers, each with a variety of substituents, are rare and challenging to achieve. Therefore, we were pleased to find that terminal azadiene **1a** reacts with aryl/alkyl and diaryl ketimines to generate diamines **6a–h** in 84–92% yield (Table 3). With

Table 3. Couplings of Azadiene 1a with Ketimines[a]



entry	product, Ar, R	yield (%)[b]	er[c]
1	**6a**, Ph, Me	90	96.5:3.5
2[d]	**6b**, 4-MeOC$_6$H$_4$, Me	84	96:4
3	**6c**, 4-MeO$_2$CC$_6$H$_4$, Me	92	>99:1
4	**6d**, 4-F$_3$CC$_6$H$_4$, Me	89	>99:1
5	**6e**, 3-BrC$_6$H$_4$, Me	91	>99:1
6	**6f**, 3-ClC$_6$H$_4$, Me	87	>99:1
7	**6g**, Ph, (CH$_2$)$_2$Ph	89	99:1
8	**6h**, Ph, Ph	86	>99:1

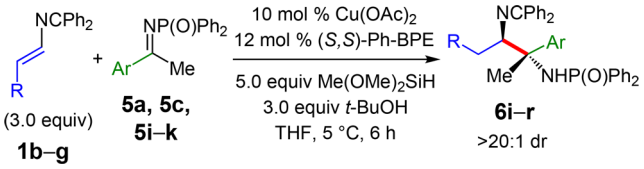
[a]Reaction under N$_2$ with 0.1 mmol imine **5**. [b,c]See Table 2. [d]Reaction at 22 °C for 24 h.

the exception of the less electrophilic, electron rich imine **5b** (entry 2), which requires higher temperature and longer reaction time, reactions proceed efficiently at 5 °C within 2 h. Transformations occur with >98% chemoselectivity for the reductive coupling regardless of imine identity. Remarkably, in all cases, the diamines are obtained in >20:1 dr (entries 1–7) and with high enantioselectivity. Notably, in addition to tolerating several aryl groups, the coupling is also permissible with longer chain alkyl groups (entry 7). The sterically encumbered benzophenone imine reacts smoothly to give diamine **6h** in 86% yield (entry 8).

Furthermore, ketimines also participate in reductive couplings with 4-substituted 2-azadienes, proceeding with ca. 60–70% chemoselectivity to furnish diamines **6i–r** as a single diastereomer and with high enantioselectivity (Table 4). Despite the steric congestion, reactions proceed to completion within 6 h at 5 °C. Product yields are improved with 10 mol % catalyst loading.[22] Variation of the ketimine's aryl substituent, including both electron rich and electron poor arenes, is tolerated in couplings with azadiene **1b** (entries 1–5). The azadiene may contain several functional groups, including heterocycles, ethers, esters, and halides that are preserved in the products (44–63% yield, entries 6–10). The versatility of the reaction partners should enable the assembly of a range of complex molecules from these diamine building blocks.

The developed azadiene–imine reductive couplings have the advantage that the amines within the products are readily differentiated (Scheme 2) as one is doubly protected as an imine (red) and the other monoprotected as the phosphinamide (blue). Either may be transformed to the amine by hydrolysis (i.e., without reduction). These qualities allow for selective functionalization of either product nitrogen. For example, deprotonation of the phosphinamide N–H of **3a** enables alkylation to deliver **7** in 84% yield while retaining the imine. Alternatively, the imine may be hydrolyzed under mildly

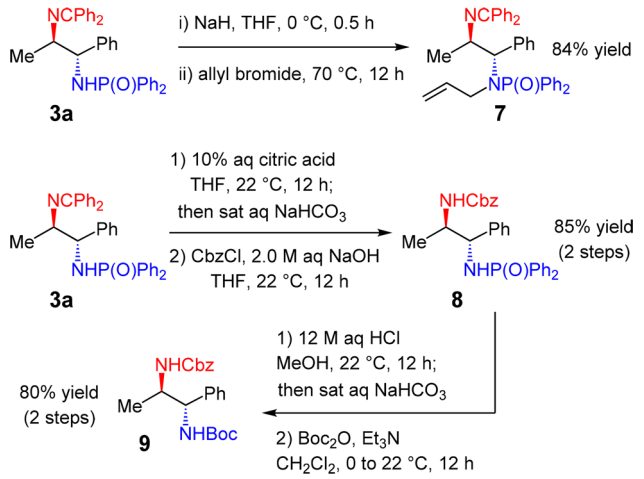
Table 4. Addition of 4-Substituted Azadienes to Ketimines[a]



entry	product, Ar, R	yield (%)[b]	er[c]
1	**6i**, Ph, (CH$_2$)$_2$Ph	62	96:4
2	**6j**, 4-MeO$_2$CC$_6$H$_4$, (CH$_2$)$_2$Ph	56	99:1
3	**6k**, 4-ClC$_6$H$_4$, (CH$_2$)$_2$Ph	62	>99:1
4	**6l**, 3,4-dioxolatoC$_6$H$_3$, (CH$_2$)$_2$Ph	59	96:4
5	**6m**, 2-naphthyl, (CH$_2$)$_2$Ph	72	98.5:1.5
6	**6n**, Ph, *n*-Bu	54	95.5:4.5
7	**6o**, Ph, (CH$_2$)$_2$(3-thiophenyl)	63	97.5:2.5
8	**6p**, Ph, (CH$_2$)$_3$OTBS	53	96.5:3.5
9	**6q**, Ph, (CH$_2$)$_4$OBz	56	97:3
10	**6r**, Ph, (CH$_2$)$_4$Cl	44	96:4

[a]Reaction under N$_2$ with 0.2 mmol imine **5**. [b,c]See Table 2.

Scheme 2. Utilizing the Products' Differentiated Amines



acidic conditions and the resulting free amine then functionalized, such as in the formation of benzyl carbamate **8** (85% yield over two steps). The phosphinamide may then be cleaved with stronger acid, enabling functionalization of the liberated amine: phosphinamide **8** is converted to *t*-butyl carbamate **9** in 80% yield (two steps).

In this work, we have shown that reductive couplings of 2-azadienes with imines are an efficient and highly stereoselective way to construct vicinal diamines, several of which are difficult to access through existing protocols and have not before succumbed to enantioselective synthesis. The methodology represents a rare example of enantioselective reductive couplings of imines as well as Cu-catalyzed reductive couplings to set vicinal heteroatom-substituted stereogenic centers. Our future efforts will concentrate on the further development of azadienes and their applications to chiral amine synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b04750.

Data for C$_{34}$H$_{30}$BrN$_2$OP (**3i**) (CIF)

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Experimental procedures, analytical data for new compounds, and X-ray crystallographic data (PDF)
NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(21) See the Supporting Information for further details.

(22) For example, with 5 mol % Cu and 6 mol % Ph-BPE, diamine **6i** in Table 4, entry 1 is isolated in only 50% yield after 12 h.

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