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Asymmetric Catalysis

Direct Enantioselective Addition of Alkynes to Imines by a Highly Efficient Palladacycle Catalyst

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Dedicated to Professor Yoshito Kishi on the occasion of his 85th birthday

Abstract: Enantiopure propargylic amines are highly valuable synthetic building blocks. Much effort has been devoted to develop methods for their preparation. The arguably most important strategy is the 1,2-addition of alkynes to imines. Despite remarkable progress, the known methods using Zn and Cu catalysts suffer from the need for high catalyst loadings, typically ranging from 2–60 mol % for neutral aldimine substrates. Here we report a planar chiral Pd complex acting as very efficient catalyst for direct asymmetric alkyne additions to imines, requiring very low catalyst loadings. Turnover numbers of up to 8700 were accomplished. Our investigation suggests that a Pd-acetylide complex is generated as a catalytically relevant intermediate by the aid of an acac ligand acting as internal catalytic base. It is shown that the catalyst is quite stable under the reaction conditions and that product inhibition is not an issue. A total of 39 examples is shown which all yielded almost enantiopure products.

Chiral enantiopure propargylic amines are building blocks of high value for the synthesis of nitrogen-containing bioactive compounds including complex natural products and active pharmaceutical ingredients.[1] They are very useful intermediates toward enantiopure compound classes such as amino acids, geometrically pure allylic amines and axially chiral allenes.[2] Arguably, the most general strategy for the preparation of highly enantioenriched propargylic amines is the asymmetric 1,2-addition of alkynes to imines.[2] In this context the pioneering studies by the Merck Research Laboratories are to be mentioned, in which metal acetylides in the presence of chiral auxiliaries were added to imines and other carbonyl derivatives with excellent enantioselectivities, providing efficient access to drugs like Efavirenz.[1a,3]

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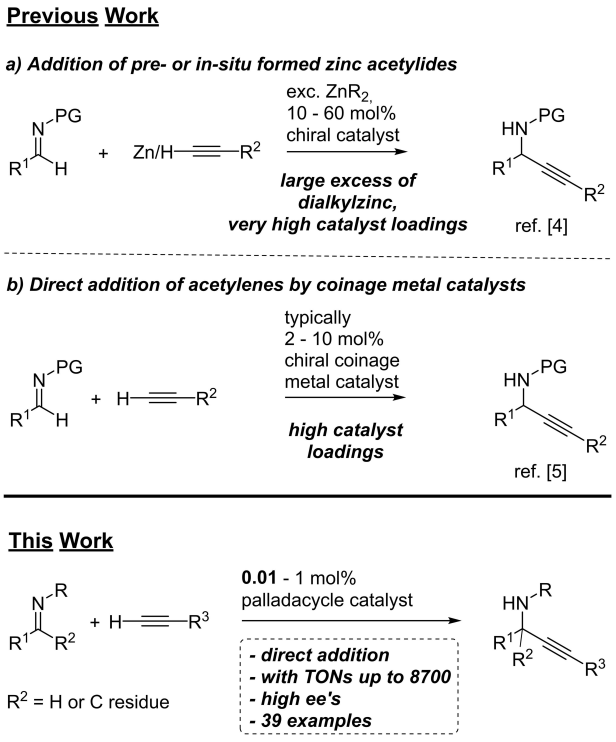
Based on this early work, various catalytic asymmetric 1,2-additions of (in situ generated) zinc acetylides to aldimines were reported (Scheme 1a).[2,4] High enantioselectivities were attained, but a large excess of organozinc reagents was necessary, often in combination with very high catalyst loadings. The use of an organometallic reagent could be avoided in direct alkyne additions using coinage metal catalysts, capable of acidifying the alkyne's C_{sp}–H bond (Scheme 1b).[5] By means of iminium species, turnover numbers (TONs) up to 660 were recently accomplished.[6] Compared to the use of aldimines, the number of publications describing direct enantioselective nucleophilic alkyne additions to ketimines is lower, adding further demands for proper reactivity and enantioselectivity.[1,7]

Here, we report a planar chiral ferrocenyl imidazoline palladacycle as very efficient, highly enantioselective catalyst for direct alkyne additions to imines (Scheme 1, bottom). Compared to previously reported work, much lower catalyst loadings could be employed resulting in TONs up to 8700.



Scheme 1. State-of-the-art compared to this work.

In *C*,*N*-palladacycles the position of the additional ligands is often controllable such that neutral ligands (or substrates) prefer to coordinate *trans* to the *N*-donor, whereas anionic ligands (or substrates) bind *trans* to the *C*-donor.[8] With a planar chiral palladacycle it was anticipated that this feature might be utilized to attain high enantioselectivity in the title reaction. Various planar chiral metallocene derived imidazoline palladacycles have previously been identified by our research group to be effective catalysts for various asymmetric reactions.[9,10]

In the present investigation, the addition of *p*-tolyl acetylene **2A** to *N*-tosyl substituted imine **1a** was initially studied as model reaction (Table 1). Early attempts suffered from very low product yields. Rather than the desired 1,2-addition, dimerization of the alkynes delivering enyne products took place. This latter reaction type was also optimized providing a regiodivergent access of enynes as recently published by us.[11]

During these early attempts, it was found that the ferrocenediyl bisimidazoline bispalladacycle **[FBIP-Cl]$_2$**[9] showed no catalytic activity in chlorobenzene at 60 °C, neither for 1,2-additions nor for the undesired alkyne dimerizations (Table 1, entry 1). Catalyst activation by silver acetate to remove the four tightly binding chloride bridges in order to facilitate substrate coordination[9] provided the desired 1,2-adduct **3aA** as a side product in 8 % yield (entry 2), yet with high enantiomeric excess (*ee* = 95 %). With Ag(acac) for catalyst activation dimerization was nearly completely supressed and **3aA** was formed as the major product in a yield of 45 % (entry 3) in nearly enantiopure form. Additional planar chiral metallocene based Pd^{II} acac complexes[9,10] were then studied (entries 4–6) revealing that the corresponding monometallic pentaphenylferrocenyl imidazoline palladacycle (**PPFIP**) complex[10a] caused no detectable alkyne dimerization and also formed almost enantiopure product (entry 6). Synthetically useful yields could be accomplished with **PPFIP-acac** at an increased reaction temperature (entry 7).

We then switched to the more electron poor imine **1b** (entries 8–10) bearing a *para*-nosyl (4-O_2N-C_6H_4-SO_2) N-substituent known as a versatile N-protective group.[12] Again, no dimerization was noticed and the product was formed in high yield and with high *ee*. A temperature of 85 °C was found to be ideal. Higher temperature led to formation of Pd black during the reaction. In all cases, catalyst activation was done prior to catalysis and the isolated acac complexes were employed. Upon treatment of **PPFIP-acac** with **1b** and **2A**, a Pd acetylide complex was detected by ESI-MS (*m/z* = 1160.23, found: 1160.23, see Supporting Information) with the expected isotopic pattern. Free acetylacetone was identified in this mixture by ^{1}H NMR indicating that acac serves as the base for the acetylide formation.

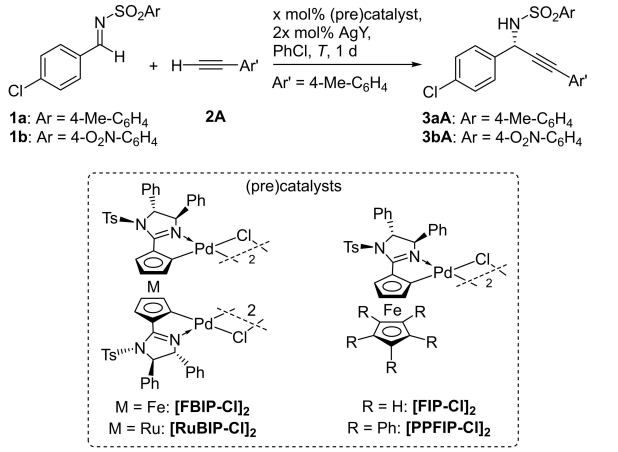
The conditions of Table 1, entry 10 were then applied to various alkyne substrates (Table 2). Aromatic alkynes bearing donor substituents (entries 1–4 and 6, 8, respectively) were all well tolerated producing the corresponding products in high yields and with excellent enantioselectivity. X-Ray single crystal structure analysis revealed an (*S*)-configuration for product **3bD**.[13] The use of aromatic alkynes bearing acceptor substituents resulted in useful yields of nearly enantiopure products (entries 7, 9, 10, 11). *Ortho*- (entries 3, 8), *meta*- (entries 2, 7) and *para*- (entries 1, 6, 10–12) as well as double-/poly-substitution (entries 4, 9) on the aromatic rings were all accepted. So was an extended π-system (entry 12) and a thiophene moiety (entry 13). Importantly, next to aromatic alkynes, also a silyl (entry 14) as well as linear and branched alkyl substituted alkynes (entries 15 and 16) could be employed.

Noteworthy is also that conjugated enynes are suitable substrates (1 mol % and 5 mol % **PPFIP-acac**, entries 17 and 18, respectively). The resulting product class, enyne carbinamines, is found in various biologically and medicinally relevant compounds like the potent naturally occurring antibacterial and anticancer agent dynemicin A.[14] In a previous study, a chiral Zn-catalyst (15–20 mol %) and $ZnMe_2$ were used to form this product type with low to good enantiocontrol (57–95 % ee) and good yields (70–96 %).[15]

In addition, the use of different aldimine substrates **1** was investigated (Table 3). It was found that aromatic aldimines bearing σ-donor (entry 2), π-donor (entry 3), σ-acceptor (entries 4, 6, 7) or π-acceptor (entry 5) substituents could be used and permitted excellent enantioselectivity.

Para- (entries 2–5), *meta*- (entry 6) and *ortho*-substituted (entry 7) aromatic imines could all be employed. Moreover,

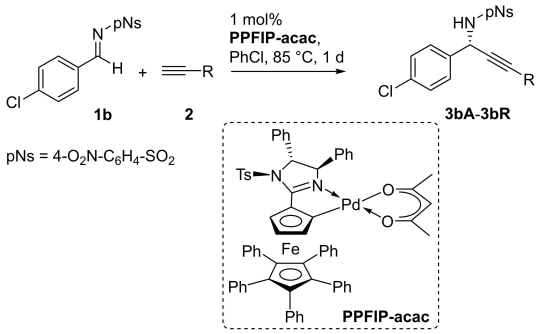
Table 1: Development of the title reaction.



Entry	Precat.	Y	*x* mol %	T [°C]	Ar	Yield dimers [%][a]	Yield **3** [%][a]	ee **3** [%][b]
1	**[FBIP-Cl]$_2$**	–	2.5	60	*p*-Tol	0	0	–
2	**[FBIP-Cl]$_2$**	OAc	2.5	60	*p*-Tol	22	8	95
3	**[FBIP-Cl]$_2$**	acac	2.5	60	*p*-Tol	4	45	99
4	**[RuBIP-Cl]$_2$**	acac	2.5	60	*p*-Tol	10	36	97
5	**[FIP-Cl]$_2$**	acac	2.5	60	*p*-Tol	4	19	97
6	**[PPFIP-Cl]$_2$**	acac	2.5	60	*p*-Tol	0	45	> 99
7	**[PPFIP-Cl]$_2$**	acac	2.5	80	*p*-Tol	3	80	99
8	**[PPFIP-Cl]$_2$**	acac	2.5	80	*p*-O_2N-C_6H_4	0	98	97
9	**[PPFIP-Cl]$_2$**	acac	0.5	80	*p*-O_2N-C_6H_4	0	82	98
10	**[PPFIP-Cl]$_2$**	acac	0.5	85	*p*-O_2N-C_6H_4	0	87	98

[a] Determined by ^{1}H NMR of the crude product using mesitylene as internal standard. [b] Determined by HPLC. OAc = acetate; acac = acetylacetonate.

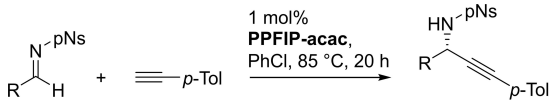
Table 2: Investigation of the alkyne scope.

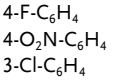


Entry	2	Product	R	Yield 3b [%][a]	ee [%][b]
1	2A	3bA	4-Me-C_6H_4	87	98
2	2B	3bB	3-Me-C_6H_4	95	>99
3	2C	3bC	2-Me-C_6H_4	98	>99
4	2D	3bD	2,4,6-$(Me)_3$-C_6H_2	99	98
5	2E	3bE	Ph	80	98
6	2F	3bF	4-MeO-C_6H_4	99	>99
7	2G	3bG	3-MeO-C_6H_4	67	>99
8	2H	3bH	2-MeO-C_6H_4	97	98
9	2I	3bI	3,5-$(MeO)_2$-C_6H_3	81	98
10	2J	3bJ	4-F-C_6H_4	76	>99
11	2K	3bK	4-Cl-C_6H_4	51	99
12	2L	3bL	2-naphthyl	78	98
13	2M	3bM	3-thienyl	94	97
14	2N	3bN	Et_3Si	43	>99[c]
15[c]	2O	3bO	$Ph(CH_2)_2$	48	>99
16	2P	3bP	cyclohexyl	88	>99
17	2Q	3bQ		92	97
18[d]	2R	3bR		43	>99

[a] Yield of isolated product. [b] Determined by HPLC. [c] Determined after product desilylation. [d] 5 mol% of catalyst were used.

Table 3: Investigation of the imine scope.



Yield	1	Product	R	Yield 3 [%][a]	ee 3 [%][b]
1	1c	3cA	Ph	90	98
2	1d	3dA	4-Me-C_6H_4	90	99
3	1e	3eA	4-MeO-C_6H_4	58	>99
4	1f	3fA	4-F-C_6H_4	93	>99
5	1g	3gA	4-O_2N-C_6H_4	95	99
6	1h	3hA	3-Cl-C_6H_4	>99	>99
7	1i	3iA	2-Cl-C_6H_4	66	97
8	1j	3jA	3,5-Cl_2-C_6H_3	95	97
9	1k	3kA	2-naphthyl	41	98
10	1l	3lA	3-furanyl	78	98
11	1m	3mA	cyclohexyl	36[c]	99
12	1n	3nA		37	95

[a] Yield of isolated product. [b] Determined by HPLC. [c] Determined by ^{1}H NMR.

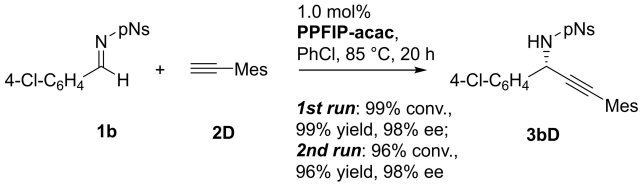
electrophiles with an extended π-system (entry 9) and an electron rich aromatic heterocycle (entry 10) were suitable reactants. An imine with a branched alkyl residue (entry 11) as well as an α,β-unsaturated imine (entry 12) also allowed for high enantioselectivity, yet yields were low in that case.

Catalyst reuse was briefly studied in the synthesis of **3bD** (Scheme 2). After the initial run, the catalyst was reisolated from the product mixture by treating the reaction mixture with Na(acac) in MeOH at 22 °C, aqueous workup and chromatographic purification. In the second run of this catalyst, similar results were attained, indicating that the catalyst is quite robust at the high reaction temperature applied.

We also studied the possibility to work with much lower catalyst loadings (Table 4). Gratifyingly, the enantioselectivity was not diminished reducing the catalyst loading from 1 to 0.025 mol %. Conversion was nearly complete after 20 h using 0.1 mol % (entry 3). With 0.05 and 0.025 mol % still high yields were accomplished (entries 4 and 5). The reactions proceeded very smoothly as conversion and yield were found to be almost identical. A TON of 8700 was achieved in entry 6 with as little as 0.01 mol % catalyst. 851 mg of **3bD** were thus prepared using 0.24 mg of catalyst.

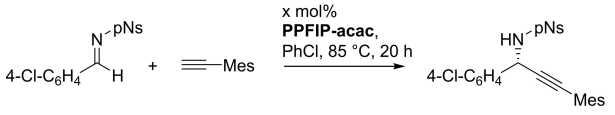
Lower catalyst loadings were also applied to the synthesis of further products providing attractive results (Scheme 3, for more results see the Supporting Information).

The catalyst robustness was studied by reaction progress kinetic analysis (RPKA) using the "same excess protocol" (Figure 1).[16] Continuous monitoring was performed for the reaction of **1b** with **2A** by ^{1}H NMR spectroscopy in 1,2-$Cl_2C_2D_4$ at 75 °C (for details see the Supporting Informa-



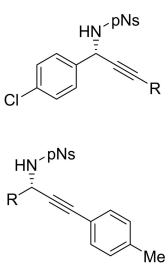
Scheme 2. Investigation of the catalyst recycling and reuse.

Table 4: Investigation of the catalyst loading.



Entry	x mol %	Conversion 1b [%][a]	Yield [%][b]	TON	ee [%][b]
1	1	99	99	99	98
2	0.5	98	97	194	98
3	0.1	99	98	980	99
4	0.05	88	88	1760	98
5[c]	0.025	86	84	3360	97
6[d]	0.01	88	87	8700	95

[a] Determined by ^{1}H NMR using mesitylene as internal standard. [b] Determined by HPLC. [c] 30 h. [d] 72 h.



3bA (R = 4-Me-C_6H_4), X = 0.5 mol%: 86%, *ee* = 98%
3bB (R = 3-Me-C_6H_4), X = 0.5 mol%: 63%, *ee* = 99%
3bC (R = 2-Me-C_6H_4), X = 0.5 mol%: 74%, *ee* = 99%
3bF (R = 4-MeO-C_6H_4), X = 0.1 mol%: 85%, *ee* = 98%
3bM (R = 3-thienyl), X = 0.5 mol%: 79%, *ee* = 97%
3bQ (R = 1-cyclohexenyl), X = 0.1 mol%: 50%, *ee* = 96%

3cA (R = Ph), X = 0.5 mol%: 80%, *ee* = 99%
3hA (R = 3-Cl-C_6H_4), X = 0.1 mol%: 74%, *ee* = 98%
3jA (R = 3,5-Cl_2-C_6H_4), X = 0.1 mol%: 67%, *ee* = 98%

Scheme 3. Application of decreased catalyst amounts (reaction conditions like in Table 4).

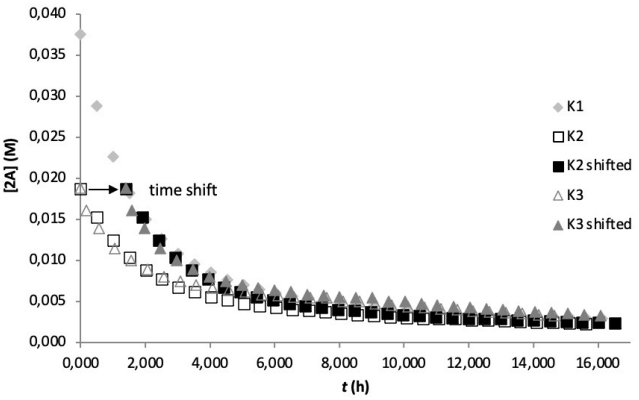


Figure 1. Reaction profiles of **2A** under the conditions of Table 5.

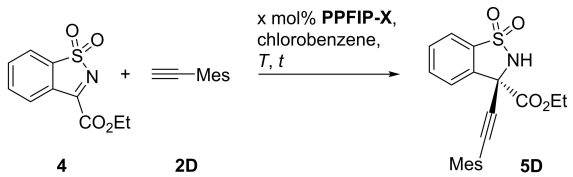
tion). Three experiments were performed using different initial concentrations (Table 5). The time-dependent decay of the concentration of **2A** is shown. Experiment K1 (Table 5) is a reference reaction. In K2 the initial concentration of **2A** and **1b** is equal to that of the reference reaction experiment when the latter had reached 50% conversion. A time shift of this curve indicates almost identical reaction rates. In K3 the conditions of K2 were used, but 50 mol% of product was added at the start, because in reference experiment K1 also 50% product was present after 50% conversion. The good overlay of all reaction profiles reveals that there is neither significant catalyst decomposition nor product inhibition.

We also briefly looked into the use of a ketimine. The addition of alkyne **2D** to cyclic iminoester **4** was selected for a screening of reaction conditions (Table 6). In this case it was found that **PPFIP-OTs** was superior to **PPFIP-acac** in terms of enantioselectivity (entries 1 and 2). However, since enantioselectivity was moderate, lower reaction temperatures were studied and at 40 °C product **5aD** was formed with high yield in almost enantiopure form (entry 4). Attractive yields were still obtained by reducing the catalyst loading to 0.5 mol% (entry 6).

Table 5: Initial reaction conditions for the RPKA "same excess" experiments.

Exp.	[**1b**] [mmol L^{-1}]	[**2A**]/ [mmol L^{-1}]	[**PPFIP-acac**]/ [mmol L^{-1}]	[**3bA**]/ [mmol L^{-1}]
K1	37.5	37.5	1.875	–
K2	18.75	18.75	1.875	–
K3	18.75	18.75	1.875	18.75

Table 6: Optimization of the asymmetric alkyne addition to ketimine **4**.



4 **2D** **5D**

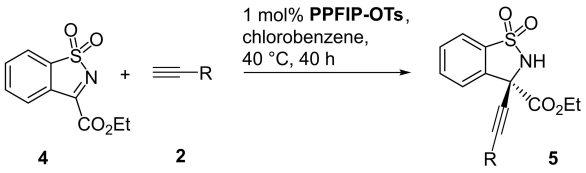
Entry	X	x mol%	T [°C]	t [h]	Yield [%][a]	ee [%][b]
1	**acac**	5	80	20	97	67
2	**OTs**	5	80	20	81	76
3	**OTs**	5	60	20	87	89
4	**OTs**	5	40	40	96	99
5	**OTs**	1	40	40	96	99
6	**OTs**	0.5	40	40	79	99

[a] Determined by ^{1}H NMR of the crude product using mesitylene as internal. [b] Determined by HPLC.

The conditions of Table 6/entry 5 were then applied to different alkynes (Table 7). Again, aromatic alkynes were well tolerated and provided nearly enantiopure products. Donor substituents on the aromatic ring had a positive impact on the yields.

In summary, we have reported a planar chiral palladacycle as very efficient catalyst for highly enantioselective direct alkyne additions to imines. Turnover numbers of up to 8700 were accomplished which is about two orders of magnitude higher than for previously reported catalysts using neutral aldimines. No additional base was required, apparently because acac serves as internal catalytic base. MS data support the assumption of a Pd-acetylide complex as catalytically relevant intermediate. Kinetic studies show that

Table 7: Asymmetric addition of acetylides to ketimine **4**.



4 **2** **5**

Entry	5	R	Yield [%][a]	ee [%][b]
1	**5D**	2,4,6-$(Me)_3$-C_6H_2	96	99
2	**5A**	4-Me-C_6H_4	94	99
3	**5E**	Ph	60	>99
4	**5F**	4-MeO-C_6H_4	97	>99
5	**5J**	4-F-C_6H_4	51	>99
6	**5M**	3-thienyl	96	99
7	**5Q**		86	99
8	**5S**	4-AcHN-C_6H_4	95	99

[a] Determined by ^{1}H NMR of the crude product using mesitylene as internal standard if not indicated otherwise. [b] Determined by HPLC.

catalyst decomposition and product inhibition are negligible. It was demonstrated that the method can be applied to a broad range of imine and alkyne substrates always providing almost enantiopure products.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: 1,2-Addition · Asymmetric Catalysis · Ferrocenes · Palladacycles · Propargylic Amines

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