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Enantioselective Nickel-Catalyzed Reductive Coupling of Alkynes and Imines

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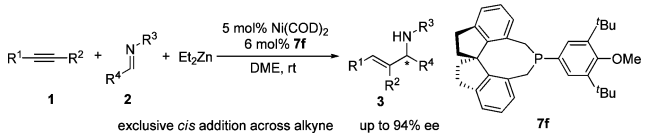
Abstract: The nickel-catalyzed reductive coupling of alkynes and imines with Et_2Zn as a reductant by using electron-rich phosphine ligands has been developed, affording various allylic amines with high yields and excellent chemoselectivities. Chiral induction was also achieved in this reductive coupling reaction when a nickel catalyst containing a chiral spiro phosphine ligand was used.

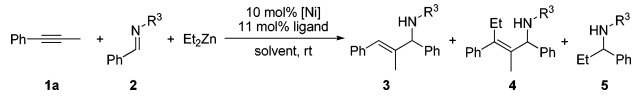
The nickel-catalyzed multicomponent coupling reaction represents one of the most efficient protocols for carbon−carbon bond formations and has drawn increasing attention.[1] Initiated by Montgomery in 1997, nickel-catalyzed three-component coupling reactions between alkynes, carbonyl compounds, and organometallics have been developed for the preparation of allylic alcohols.[2] However, the nickel-catalyzed coupling reaction of alkynes with imines are difficult to perform because imines are weaker electrophiles than aldehydes and, furthermore, the allylic amine products may deactivate or decompose the nickel catalyst. The first breakthrough in the nickel-catalyzed coupling reaction of alkynes with imines was made by Jamison and co-workers.[3] They achieved the alkylative coupling (AC) of disubstituted alkynes, *N*-alkyl imines, and organoboron reagents to produce allylic amines with a tetrasubstituted olefin moiety with good to excellent yields, high regioselectivities, and moderate to high enantioselectivities. However, the reductive coupling (RC) of alkynes with imines, which produces allylic amines with a trisubstituted olefin moiety, is simply a side reaction in Jamison's system. To date, the nickel-catalyzed RC of alkynes with imines has not been achieved.[4] In 2005, Krische reported rhodium-catalyzed diastereoselective couplings of 1,3-enynes and 1,3-diynes with ethyl *N*-sulfinyliminoacetates employing H_2 as a reductant.[5] Recently, highly enantioselective iridium-catalyzed reductive coupling of dialkyl-substituted alkynes with *N*-sulfonyl-imines and rhodium-catalyzed couplings of acetylene and imines have also been developed by the same group.[6] Here we report the nickel-catalyzed reductive coupling reaction of aryl-substituted alkynes, imines, and Et_2Zn, providing allylic amines in high yields (up to 96%) and excellent chemoselectivities (RC/AC up to 42:1). We also accomplished an asymmetric version of this reaction by using chiral spiro phosphine ligands, and high enantioselectivities (up to 94% ee) were achieved (Scheme 1).

Scheme 1



We initially conducted the nickel-catalyzed reductive coupling of 1-phenyl-1-propyne (**1a**) with imines by using Et_2Zn as a reducing agent. Fortuitously, the *N*-tosyl protected imine **2a** underwent the three-component coupling reaction smoothly in the presence of 10 mol % nickel catalyst formed in situ from $Ni(acac)_2$ and PPh_3. The expected reductive coupling product **3a** was isolated along with the alkylative coupling product **4a** and the direct Et_2Zn addition byproduct **5a** in a ratio of **3/4/5** = 2:1:1 (Table 1, entry 1). Other organometallic reagents such as Et_3B, Et_3Al, and $HSiEt_3$ were ineffective in this reaction. Replacement of the tosyl group with another protecting group such as phenyl, methyl, or $P(O)Ph_2$ was also unsuccessful for increasing the yield and chemoselectivity of the reaction. Both monodentate and bidentate phosphorus ligands can promote the coupling reaction; however, only the less-hindered and electron-rich ligand *n*-Bu_3P yielded the reductive coupling product in good yield (66%) and excellent chemoselectivity (**3/4/5** = 23:1:3) (entry 4). When the catalyst precursor $Ni(COD)_2$ was used the yield increased to 86% (entry 6). Under the optimal conditions, the catalyst loading was reduced to 5 mol % and the ratio of the alkyne, imine, and Et_2Zn was lowered to 2:1:1 (entry 8). Imines with other sulfonyl protecting groups were also suitable substrates (entries 9 and 10). Because the *N*,*N*-dimethylsulfamoyl protecting group is easy to remove,[7] we chose imine **2c** for further investigation.

Table 1. Nickel-Catalyzed Three-Component Reductive Coupling of 1-Phenyl-1-propyne, Imine, and $ZnEt_2$[a]



entry	R^3	[Ni]	ligand	solvent	time (h)	**3/4/5** [b]	yield of **3** (%) [c]
1	Ts (**2a**)	$Ni(acac)_2$	Ph_3P	THF	1	2:1:1	36
2	Ts (**2a**)	$Ni(acac)_2$	$(OPh)_3P$	THF	1	2:1:10	5
3	Ts (**2a**)	$Ni(acac)_2$	$(c\text{-}C_6H_{11})_3P$	THF	1	5:1:0.3	48
4	Ts (**2a**)	$Ni(acac)_2$	*n*-Bu_3P	THF	1	23:1:3	66
5	Ts (**2a**)	$Ni(acac)_2$	dppe [d]	THF	8	1:1:1	15
6	Ts (**2a**)	$Ni(COD)_2$	*n*-Bu_3P	THF	1	24:1:3	86
7 [e]	Ts (**2a**)	$Ni(COD)_2$	*n*-Bu_3P	DME	1	27:1:3	90
8 [e,f]	Ts (**2a**)	$Ni(COD)_2$	*n*-Bu_3P	DME	2	23:1:2	82
9 [e,f]	 (**2b**)	$Ni(COD)_2$	*n*-Bu_3P	DME	2	22:1:1	88
10 [e,f]	 (**2c**)	$Ni(COD)_2$	*n*-Bu_3P	DME	2	28:1:1	87

[a] Reaction conditions: [Ni]/ligand/**1a**/**2**/Et_2Zn = 0.04/0.044/1.6/0.4/0.96 (mmol), in 2 mL of solvent at room temperature. [b] Determined by ^1H NMR. [c] Determined by ^1H NMR (see Supporting Information for details). [d] 1,2-Di(diphenylphosphino)ethane. [e] **1a**/**2**/Et_2Zn = 2:1:1. [f] 5 mol % catalyst was used.

The reductive coupling reaction was applicable to a broad range of substrates. Benzaldehyde-derived imines with different substituent patterns underwent reductive coupling with 1-phenyl-1-propyne (**1a**) under the optimal reaction conditions to produce various allylic amines with good to excellent yields (69−96%) and high to excellent chemoselectivities (**3/4** ranged from 15:1 to 42:1) (Table

Table 2. Nickel-Catalyzed Reductive Coupling of Alkynes with Imines[a]

entry	alkyne: R^1, R^2	imine: R^4	product	**3/4**	yield of **3** (%)
1	Ph, Me (**1a**)	Ph (**2c**)	**3ac**	28:1	87
2	Ph, Me (**1a**)	*o*-$MeOC_6H_4$ (**2d**)	**3ad**	15:1	74
3	Ph, Me (**1a**)	*o*-MeC_6H_4 (**2e**)	**3ae**	22:1	74
4	Ph, Me (**1a**)	*o*-ClC_6H_4 (**2f**)	**3af**	30:1	85
5	Ph, Me (**1a**)	*m*-MeC_6H_4 (**2g**)	**3ag**	27:1	91
6	Ph, Me (**1a**)	*m*-ClC_6H_4 (**2h**)	**3ah**	30:1	88
7	Ph, Me (**1a**)	*p*-$MeOC_6H_4$ (**2i**)	**3ai**	25:1	69
8	Ph, Me (**1a**)	*p*-MeC_6H_4 (**2j**)	**3aj**	27:1	84
9	Ph, Me (**1a**)	*p*-FC_6H_4 (**2k**)	**3ak**	29:1	83
10	Ph, Me (**1a**)	*p*-ClC_6H_4 (**2l**)	**3al**	30:1	96
11	Ph, Me (**1a**)	*p*-$CF_3C_6H_4$ (**2m**)	**3am**	42:1	80
12	Ph, Me (**1a**)	3,4-$Cl_2C_6H_3$ (**2n**)	**3an**	37:1	85
13	Ph, Me (**1a**)	1-naphthyl (**2o**)	**3ao**	26:1	82
14	Ph, Me (**1a**)	2-naphthyl (**2p**)	**3ap**	25:1	87
15	Ph, Me (**1a**)	*n*-Pr (**2q**)[b]	**3aq**	22:1	51
16	Ph, Me (**1a**)	*i*-Pr (**2r**)[b]	**3ar**	6:1	50
17	Ph, Me (**1a**)	*c*-C_6H_{11} (**2s**)[b]	**3as**	16:1	59
18	Ph, Et (**1b**)	Ph (**2c**)	**3bc**	19:1	70
19	Ph, Ph (**1c**)	Ph (**2c**)	**3cc**	18:1	81
20[c]	Et, Et (**1d**)	Ph (**2c**)	**3dc**	14:1	56

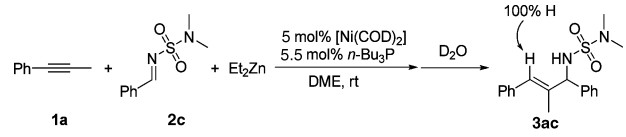
[a] Unless otherwise noted, reaction conditions were the same as those in Table 1, entry 10. All reactions complete within 2 h. [b] Protecting group is Ts. [c] [Ni]/*n*-Bu_3P/**1d/2c**/ Et_2Zn = 0.02/0.04/0.48/0.4/0.96 (mmol), 80 °C.

2, entries 1−12). The imines with 1-naphthyl (**2o**) and 2-naphthyl (**2p**) substituents exhibited properties that were similar to those of imine **2c** in the reductive coupling reaction (entries 13 and 14). The imines derived from aliphatic aldehydes (**2q**-**2s**) were less reactive under the standard reaction conditions, affording the reductive coupling products in only moderate yields (entries 15−17). In addition to 1-phenyl-1-propyne (**1a**), all other tested alkynes were suitable substrates for the reaction, although the aliphatic alkyne afforded a lower yield (entries 18−20).

The asymmetric version of the nickel-catalyzed reductive coupling was then studied. After systematic evaluation of various chiral ligands,[8] we found that the spiro phosphine **7f** was the most efficient ligand in terms of yield (74%), chemoselectivity (**3/4** = 9:1), and enantioselectivity (87% ee) (Table 3, entry 1). When $Ni(COD)_2$/(*R*)-**7f** was used as a catalyst, all the tested imines derived from aromatic aldehydes underwent the coupling reaction smoothly to produce the corresponding allylic amines with good yields and high to excellent selectivities. Except for *o*-methoxyphenyl imine **2d** and *o*-chlorophenyl imine **2f**, which interestingly afforded the highest (94% ee) and lowest (76% ee) enantioselectivities, respectively, the other imines derived from aromatic aldehydes gave almost the same level of enantioselectivity (82−89% ee) (entries 1, 3, 5−14). The coupling of *o*-methylphenyl imine **2e** gave the highest chemoselectivity (**3/4** = 16:1) (entry 3), whereas 1-naphthyl imine **2o** gave the lowest chemoselectivity (**3/4** = 4:1) (entry 13). In contrast, imines derived from aliphatic aldehydes give lower enantioselectivities (entries 15 and 16). Changing the R^2 group of the alkyne had almost no influence on the reactivity and enantioselectivity of the reaction (entries 17 and 18). Dialkyl substituted hex-3-yne can also proceed in the coupling reaction but afforded a 1:1 mixture of products **3** and **4** (entry 19). Most of the reductive coupling products were solids and were easily purified by recrystallization (entries 1, 5, and 10). Furthermore, the *N*,*N*-dimethylsulfamoyl group of products was easily removed by means of the published procedure.[7,8] The absolute configuration of **3ac** was determined to be *S* by chemical correlation.[8]

An isotope-labeling experiment showed that the transferred hydrogen was most likely from the ethyl group of Et_2Zn (Scheme 2). The studies for accurate mechanism are undergoing in this laboratory and will be reported in due course.

Scheme 2



In summary, highly efficient nickel-catalyzed reductive coupling of alkynes and imines with Et_2Zn as a reductant has been realized. The asymmetric version of this reaction was also achieved in high enantioselectivity by using a chiral spiro phosphine ligand. The nickel catalyst developed in this study favors the aromatic alkynes and provides a complement to Krische's iridium catalyst which prefers aliphatic alkynes.

Table 3. Nickel-Catalyzed Asymmetric Reductive Coupling of Alkynes with Imines[a]

entry	alkyne: R^1, R^2	imine: R^4	product	**3/4**	yield of **3** (%)	ee of **3**(%)
1	Ph, Me (**1a**)	Ph (**2c**)	**3ac**	9:1	74(64)[b]	87(96)[b]
2	Ph, Me (**1a**)	*o*-$MeOC_6H_4$ (**2d**)	**3ad**	7:1	63	94
3	Ph, Me (**1a**)	*o*-MeC_6H_4 (**2e**)	**3ae**	16:1	71	82
4	Ph, Me (**1a**)	*o*-ClC_6H_4 (**2f**)	**3af**	11:1	80	76
5	Ph, Me (**1a**)	*m*-MeC_6H_4 (**2g**)	**3ag**	12:1	77(66)[b]	86(98)[b]
6	Ph, Me (**1a**)	*m*-ClC_6H_4 (**2h**)	**3ah**	11:1	75	85
7	Ph, Me (**1a**)	*p*-$MeOC_6H_4$ (**2i**)	**3ai**	14:1	68	89
8	Ph, Me (**1a**)	*p*-MeC_6H_4 (**2j**)	**3aj**	13:1	71	86
9	Ph, Me (**1a**)	*p*-FC_6H_4 (**2k**)	**3ak**	9:1	72	86
10	Ph, Me (**1a**)	*p*-ClC_6H_4 (**2l**)	**3al**	7:1	78(61)[b]	85(96)[b]
11	Ph, Me (**1a**)	*p*-$CF_3C_6H_4$ (**2m**)	**3am**	6:1	67	84
12	Ph, Me (**1a**)	3,4-$Cl_2C_6H_3$ (**2n**)	**3an**	9:1	69	87
13	Ph, Me (**1a**)	1-naphthyl (**2o**)	**3ao**	4:1	62	88
14	Ph, Me (**1a**)	2-naphthyl (**2p**)	**3ap**	8:1	80	87
15	Ph, Me (**1a**)	*n*-Pr (**2q**)[c]	**3aq**	6:1	65	11
16	Ph, Me (**1a**)	*c*-C_6H_{11} (**2s**)[c]	**3as**	6:1	51	9
17	Ph, Et (**1b**)	Ph (**2c**)	**3bc**	9:1	81	88
18	Ph, Ph (**1c**)	Ph (**2c**)	**3cc**	7:1	62	86
19	Et, Et (**1d**)	Ph (**2c**)	**3dc**	1:1	41(41)[d]	67(84)[d]

[a] Reaction conditions: $Ni(COD)_2$/(*R*)-**7f**/**1**/**2**/$ZnEt_2$ = 0.0075/0.009/0.3/0.15/0.36 (mmol) in 0.75 mL of DME at rt. All reactions complete within 3 h. [b] Data in parentheses are those after recrystallization. [c] Protecting group is Ts. [d] Data in parentheses are for alkylative product **4dc**.

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Supporting Information Available: Detailed experimental procedures, the synthetic methods and analytic data for new ligands, and the analytic data and ee values for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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