Imine Chemistry

Asymmetric Catalytic Coupling of Organoboranes, Alkynes, and Imines with a Removable (Trialkylsilyloxy)ethyl Group—Direct Access to Enantiomerically Pure Primary Allylic Amines**

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Enantiomerically enriched allylic amines are frequently used as synthetic intermediates, auxiliaries, and resolving agents in the synthesis of both natural and nonnatural compounds.[1] Herein we report the first highly enantioselective catalytic synthesis of allylic amines from alkynes, imines, and organoboranes. Catalyzed by a complex derived from $[Ni(cod)_2]$ and a P-chiral ferrocenyl phosphane, this three-component process provides enantiomerically enriched, tetrasubstituted allylic amines in a single operation. A (*tert*-butyldimethylsilyloxy)ethyl ($TBSOCH_2CH_2$) group on the imine nitrogen not only maximizes reactivity and selectivity in these transformations, but also is easily removed after the coupling reaction, thus providing direct access to versatile primary allylic amines that can be recrystallized to optical purity.[2]

Several catalytic asymmetric syntheses of allylic alcohols from alkynes and aldehydes in high enantioselectivities have been reported,[3] but comparable success has not been achieved for the corresponding synthesis of allylic amines from imines.[4,5] Buchwald and co-workers have reported that stoichiometric reactions of chiral *ansa*-zirconocene imine complexes and alkynes provide trisubstituted allylic amines in high enantiomeric excess.[6] Bisoxazolines and (−)-sparteine promote enantioselective additions of organolithium reagents to imines (69–91% *ee*); however, reactions catalytic in the ligand result in lower selectivity (51–82% *ee*).[7] A complementary strategy was recently reported by Hayashi and Ishigedani involving the rhodium-catalyzed asymmetric addition of aryl stannanes to α,β-unsaturated imines.[8]

We recently reported a nickel-catalyzed three-component coupling reaction of alkynes, imines, and organoboron reagents (boronic acids and organoboranes), which affords

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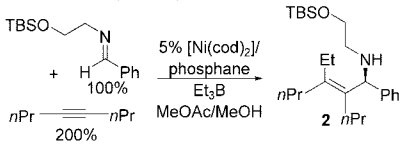
tetrasubstituted allylic amines.[9] Good to excellent yields, high regioselectivity, and complete *E*/*Z* selectivity (*cis* addition to the alkyne) are observed when electron-rich tri(*sec*-alkyl) phosphane ligands were employed. Although our research group has recently reported that nickel-catalyzed coupling reactions of certain alkynes and aldehydes in the presence of neomenthyldiphenylphosphane afford allylic alcohols in excellent enantioselectivities and yields,[3a] this ligand is ineffective in analogous reactions of imines.[10]

An extensive evaluation of a large number and variety of chiral monophosphanes[11] demonstrated that P-chiral ferrocenyl phosphanes afforded the desired allylic amines in good yields and enantioselectivities, as long as the group on nitrogen was aliphatic in nature (Table 1).[12] These ligands,

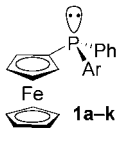
Table 1: Evaluation of P-chiral ferrocenyl phosphanes in the catalytic three-component assembly of allylic amines.[a]



Entry	Phosphane	Yield [%]	*ee*[b]
1	**1a**	88	75
2	**1b**	90	80
3	**1c**	60	75
4	**1d**	**85**	**89**
5	**1e**	19	45
6	**1f**	85	75
7	**1g**	25	77
8	**1h**	20	45
9	**1i**	64	54
10	**1j**	41	41
11	**1k**	73	51

[a] See Experimental Section for details. [b] Determined by HPLC (Chiralcel OD, results with **1d** are highlighted in bold).

1a–**k**, were synthesized in enantiomerically pure form by a modification of Jugé's ephedrine-based method.[3b,13] A notable feature of this ligand family is that, in contrast to trialkyl phosphane ligands, reductive coupling by-products are not observed (transfer of H instead of Et from Et_3B).[9]

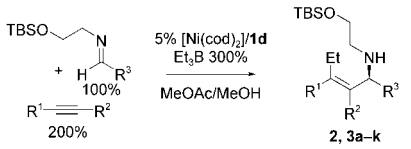


	Ar		Ar
a	*o*-tolyl	**g**	2-*i*Pr-5-MeC_6H_3
b	2-EtC_6H_4	**h**	3,5-*t*Bu$_2C_6H_3$
c	2-*n*BuC_6H_4	**i**	*o*-anisyl
d	2-*i*PrC_6H_4	**j**	2-EtOC_6H_4
e	*o*-biphenylyl	**k**	2-*i*PrOC_6H_4
f	2,5-Me$_2C_6H_3$		

Remarkably, desymmetrization of $FcPPh_2$ by replacing H with Me at the *ortho* position of one of the phenyl groups (i.e. **1a**) provided allylic amine **2** in 75% *ee* and very good yield (Table 1, entry 1). We further observed that enantioselectivity tended to increase as the steric bulk in this *ortho* position increased (Table 1, entries 2–4), up to a point. A phenyl substituent in the *ortho* position (i.e. Ar = *o*-biphenylyl (**1e**), entry 5) led to a severely diminished yield (19%) and enantioselectivity (45%). Unfortunately, all efforts to synthesize more sterically demanding phosphanes (for example Ar = 2-*t*BuC_6H_4, 2,6-Me$_2C_6H_3$) were unsuccessful.[14] Furthermore, lower yields and enantioselectivities were obtained with other substitution patterns (Table 1, entries 6–8) and with ligands possessing alkoxy groups in the *ortho* position (Table 1, entries 9–11). Modifications of ligand/metal stoichiometry, solvent composition, and modes of reagent addition decreased efficacy and/or selectivity. The highest yields and enantioselectivities were observed with the portionwise addition of the alkyne and Et_3B (as a solution in MeOAc; see Experimental Section for details).

Ligand **1d** proved to be the most selective phosphane in these studies, and it also allowed the preparation of allylic amines from a variety of substrate combinations in moderate to very good enantioselectivities (Table 2). Both symmetrical

Table 2: Enantiomerically enriched allylic amines prepared through catalytic intermolecular coupling of an alkyne, an imine, and triethylborane.[a]



Entry	R^1	R^2	R^3	Product	Yield [%] (regio)[b]	*ee* [%][c]
1	*n*Pr	*n*Pr	Ph	**2**	85	89
2	*n*Bu	*n*Bu	Ph	**3a**	83	89
3	Et	Et	Ph	**3b**	89	83
4	*n*Pr	*n*Pr	*o*-tolyl	**3c**	74	85
5	*n*Pr	*n*Pr	*p*-anisyl	**3d**	75	82
6	*n*Pr	*n*Pr	*p*-$CF_3C_6H_4$	**3e**	91	85
7	*n*Pr	*n*Pr	2-naphthyl	**3f**	90	73
8	nPr	*n*Pr		**3g**	95	73
9	Et	Et	*c*-C_6H_{11}	**3h**	53	51
10	Ph	Me	Ph	**3i**	45 (80:20)	84
11	Ph	Et	Ph	**3j**	62 (>98:2)	71
12	2-naphthyl	Me	Ph	**3k**	42 (85:15)	70

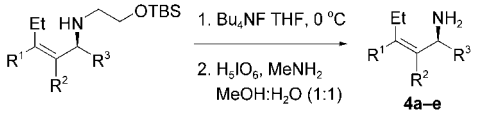
[a] See Experimental Section for details. [b] Determined by ^{1}H NMR. [c] Enantiomeric excess of the major product determined by HPLC or GC.

dialkyl acetylenes (entries 1–9) and unsymmetrical alkynes of the general form Ar–C≡C–Alkyl (entries 10–12) are effective in these reactions, the latter allowing the preparation of enantiomerically enriched tetrasubstituted allylic amines with four different substituents on the alkene with good to complete control of olefin geometry and regioselectivity. Furthermore, several aromatic imines undergo this three-component coupling reaction to give the products in both high enantiomeric excess and yield (Table 2, entries 4–8). No significant difference in enantioselectivity was observed with electron-donating (Table 2, entries 4 and 5) or elec-

tron-withdrawing (entry 6) substituents on the phenyl group; however, imines derived from 2-naphthaldehyde or piperonal were less selective (entries 7 and 8). Notably, even an enolizable aliphatic imine undergoes catalytic asymmetric three-component coupling in moderate enantioselectivity and yield (Table 2, entry 9).[15]

The $TBSOCH_2CH_2$-protected allylic amines are readily deprotected by a two-step protocol: deprotection of the TBS ether with Bu_4NF, followed by oxidative cleavage of the resulting 2-amino alcohol (Table 3).[16] Since the optical purity is conserved in this reaction sequence, enantiomerically enriched tetrasubstituted primary allylic amines are obtained in good overall yield and good enantiomeric excess. Several chiral 2-amino alcohols (mostly derived from amino acids) have been used as auxiliaries for diastereoselective imine addition reactions,[17] but this is the first example of a catalytic, enantioselective addition to imines derived from an *achiral* 2-amino alcohol. These primary allylic amines can be recrystallized to optical purity as maleic acid salts [Eq. (1)].

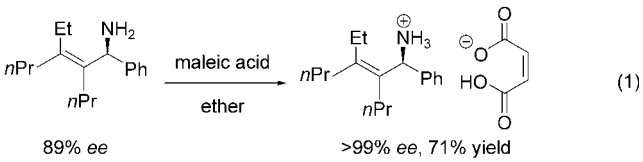
Table 3: Deprotection of $TBSOCH_2CH_2$-protected allylic amines.



4a–e

Entry	R^1	R^2	R^3	Product	Yield [%]	*ee* [%]
1	*n*Pr	*n*Pr	Ph	**4a**	73	89
2	*n*Pr	*n*Pr	o-tolyl	**4b**	66	85
3	*n*Pr	*n*Pr	2-naphthyl	**4c**	59	76
4	*n*Pr	*n*Pr		**4d**	68	73
5	Ph	Me	Ph	**4e**	63	84

[a] Enantiomeric excess of the major product, determined by HPLC.



(1)

In conclusion, the above catalytic asymmetric transformation provides enantiomerically enriched tetrasubstituted allylic amines in a single step, and high reaction yields (up to 95%) and good enantioselectivities (up to 89% *ee*) are observed in many cases. Furthermore, removal of the (*tert*-butyldimethylsilyloxy)ethyl protecting group provides direct access to versatile primary allylic amines that can be further recrystallized to >99% *ee*.

Experimental Section

General procedure: The imine (0.5 mmol) and alkyne (0.20 mmol) were added to a solution of Et_3B (0.30 mmol, 3 M in MeOAc), $[Ni(cod)_2]$ (0.025 mmol), phosphane ligand (0.025 mmol), and MeOH (2.5 mL) under Ar. Four equal portions of additional Et_3B (4 × 0.30 mmol) and alkyne (4 × 0.20 mmol) were added every 10 min, and the reaction was stirred an additional 12 h. Concentration in vacuo and purification over silica gel (hexanes/EtOAc) afforded the allylic amines. Enantioselectivities were measured by HPLC (Chiralcel OD or AD columns) or GC (Chiraldex B-PH, B-DA, and G-TA capillary columns).

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