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The First Catalytic Asymmetric Allylation of Imines with the Tetraallylsilane−TBAF−MeOH System, Using the Chiral Bis-π-allylpalladium Complex

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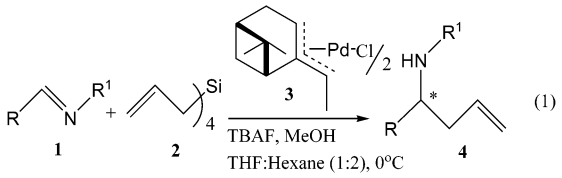
The asymmetric allylation of imines with use of catalytic transition metals with chiral ligands should be a new frontier of the enantioselective C−C bond formation. So far allyltrimethylsilane, allyltrichlorosilane, and allyltrimethoxysilane have been commonly employed with use of either silane activators or dual silane−imine activators. However, tetraallylsilane is untouched in the allylation of aldimines. The first allylation of aldimines with the tetraallylsilane−TBAF−MeOH system with use of the bis-π-allylpalladium catalyst under catalytic, non-Lewis acid, essentially neutral and very mild reaction conditions has been achieved. The reaction is triggered by dual activation/promotion by TBAF and MeOH in which the fluoride anion activates the C−Si bond cleavage and MeOH promotes the facile protonation of intermediate palladium amide. Thus, the synthesis of chiral homoallylamines is achieved in a shorter reaction time and higher yields and enantioselectivities through an efficient, general, and reproducible allylation protocol for imines.

Introduction

Allylations of imines **1** (eq 1) or iminium species with



(1)

allylic silane or tin reagents are one of the most effective methods for the introduction of an amino group into carbon skeletons.[1] Tin-based reagents are less stable, more reactive, and significantly toxic. Our laboratory reported the first catalytic asymmetric allylation of imines in 1998 using allyltributylstannane in the presence of chiral π-allylpalladium complex **3**.[2] Several reports have been documented on allylation of imines with silanes or tin-based reagents.[3] Lewis or Bronstead acids have been employed for imine activation.[1] It is also reported that fluoride anion or alkoxides also activate the C−Si bond of allylsilane by coordination to the silicon atom.[4] Allylation of *N*-acyl hydrazones is also well established.[5] Our earlier work with allyltributylstannane and allyltrimethylsilane gave homoallylamines up to 84% ee.[2] This left enough opportunity for further improvement of both chemical yields and enantioselectivity. After careful investigation we found the catalyst used in our earlier work was a mixture of two stereoisomers. We have separated the undesired isomer and achieved a highest separation ratio of >400:1.[6] Better results were obtained with this catalyst and so we believe that this novel catalytic manifold arises in part from refining catalyst **3**. These achievements created a quest to search a better allylating agent that is less toxic than the stannanes and more efficient in reaction with imines to give correspond-

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(4) For leading references on fluoride- or alkoxide-promoted allylation of imines with allylsilanes see: (a) Yamasaki, S.; Fujii, K.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 6536. (b) Wang, D.-K.; Zhou, Y.-G.; Tang, Y.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* **1999**, *64*, 4233. (c) Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1996**, *61*, 6901. (d) Sakurai, H. *Synlett* **1989**, 1. Also see ref 2c.

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(6) The catalyst **3** was separated from its stereoisomer, which arises from the starting olefin (1:1, *E*/*Z* mixture) from which this complex is prepared. Repeated recrystallizations gave the complex **3** having $[\alpha]^{22}_{D}$ −20.9 (*c* 0.4 in $CHCl_3$). This is the highest optical purity of complex **3** that we have achieved so far in our laboratory (more details in the Supporting Information).

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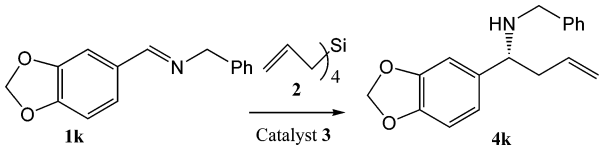
TABLE 1. Optimization of Conditions for the Following Reaction[a]



entry	solvent	equiv of silane	additive (mol %)	temp (°C)	time (h)	% yield of **4k**	% ee[b] of **4k**
1	THF	2	no additive	0	96	no reaction	
2	THF	2	H_2O (100)	0	96	no reaction	
3	THF	2	TBAF (50)[c]	0	32	40	72
4	DMF	2	TBAF (50)	0	32	28	84
5	THF:hexane (1:2)	2	TBAF (50)	0	18	79	86
6	THF:hexane (1:2)	1.2	TBACl (50)	0	96	no reaction	
7	THF:hexane (1:2)	1.2	TBAI (50)	0	96	no reaction	
8	THF:hexane (1:2)	1.2	CsF (50)	0	96	no reaction	
9	THF:hexane (1:2)	1.2	TBAF (50)	0	18	80	89
10	THF:hexane (1:2)	0.5	TBAF (50)	0	18	70	88
11	THF:hexane (1:2)	1.2	TBAF (25)	0	20	80	90
12	THF:hexane (1:2)	1.2	TBAF (10)	0	32	33	86
13	THF:hexane (1:2)	1.2	TBAF (50) + M. Sieves[d]	0	18	61	86
14	THF:hexane (1:2)	1.2	TBAF (25) + MeOH (100)	0	15	83 (88)[e]	90
15	THF:hexane (1:2)	1.2	TBAF (25)	rt	16	45	82
16	THF:hexane (1:2)	1.2	TBAF F (25)	−10	32	66	87

[a] All reactions were carried out with 5 mol % catalyst **3**. [b] Ee was determined by HPLC. [c] 1 M solution in THF was used. [d] 100 mg/mmol was used. [e] Yield of the amine product when the reaction mixture was loaded directly on silica gel column without workup.

ing homoallylamines in a shorter reaction time and higher yields and enantioselectivities. So far allyltrimethylsilane, allyltrichlorosilane, and allyltrimethoxysilane have been commonly employed with use of either silane activators or dual silane−imine activators. We tried all of these allylsilane reagents and the best results were obtained with tetraallylsilane.[7] Moreover, tetraallylsilane is untouched in the allylation of aldimines.[7] We wish to report in detail the first catalytic asymmetric allylation of aldimines with tetraallylsilane **2** using catalyst **3** (5 mol %) in the presence of TBAF (25 mol %) and MeOH (1 equiv) (eq 1). The present method provides higher chemical yields and enantioselectivities in much shorter reaction time, compared to the previously reported procedure.[2]

Results and Discussion

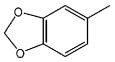
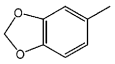
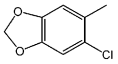
In our laboratory we have refined π-allylpalladium complex **3** by repeated recrystallization and separated it from its undesired stereoisomers.[6] Using this catalyst we first optimized the reaction conditions for allylation of imine **1k** in the presence of **3** (5 mol %) to give **4k** as shown in Table 1. The initial investigations with tetraallylsilane revealed that TBAF is an efficient promoter of C−Si bond cleavage and is the key to the reaction, while others like H_2O,[8] TBACl, TBAI, and CsF are unsuccessful (entries 1−8). A pronounced solvent effect was observed with THF:hexane (1:2) standing out as the most efficient solvent combination in terms of conversion and enantioselectivity, while only THF or DMF was not as effective (entries 1−5). Lowering the concentration of tetraallylsilane from 2 to 1.2 equiv worked very well (entry 9). However, the use of 0.5 equiv of tetraallylsilane gave a slight decrease in yield of amine **4k**, though a similar level of enantioselectivity was observed (entry 10), indicating that more than one allyl group can be transferred. Next we attempted to lower the concentration of TBAF. Better results were obtained with 25 mol % of TBAF (entry 11). However, a remarkable decrease in yields of amine **4k** was observed with further lowering the concentration of TBAF to 10 mol % (entry 12). But it still indicates that a catalytic amount of fluoride anion is sufficient for the allylation reaction to proceed. Further optimization revealed that molecular sieves are not required to dry the TBAF solution as it gave a lower yield in comparison to reaction without it (entry 13). However, addition of a protonating solvent such as MeOH (1 equiv) gave a remarkably shorter reaction time and higher yields with a similar outcome of enantioselectivity (90% ee) of product amine **4k** (entry 14). Reactions at room temperature or at a lower temperature of −10 °C gave inferior results with regard to both yield and enantioselectivity (entries 15 and 16). Thus, tertaallylsilane (1.2 equiv), TBAF (25 mol %), MeOH (1 equiv), and **3** (5 mol %) in THF:hexane (1:2) at 0 °C stand out as the optimum conditions for the allylation reaction (entry 14). We speculate that this reaction proceeds with dual activation/promotion in which the fluoride anion activates the C−Si bond cleavage and MeOH promotes the facile protonation of the intermediate palladium amide. Thus, this documents the first catalytic asymmetric allylation of aldimines with use of tetraallylsilane, which is less toxic compared with allyltin compounds.

The scope of this allylation protocol with the tetraallylsilane−TBAF−MeOH system and chiral π-allylpalla-

(7) Results on the various allylsilane reagents tried are given in the Supporting Information. There is one report of tetraallylsilane addition to chiral *N*-acylhydrazones, in which a chirality exists in the substrate and the asymmetric induction arises from chirality transfer of the substrate (ref 5d). Neither tetraallylsilane addition to aldimines nor catalytic asymmetric addition of it has been reported.

(8) Water was employed as it was found to promote allylation in the case of allyltributylstannane but this was not the case with silanes. Fernandes, R. A.; Stimac, A.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 14133.

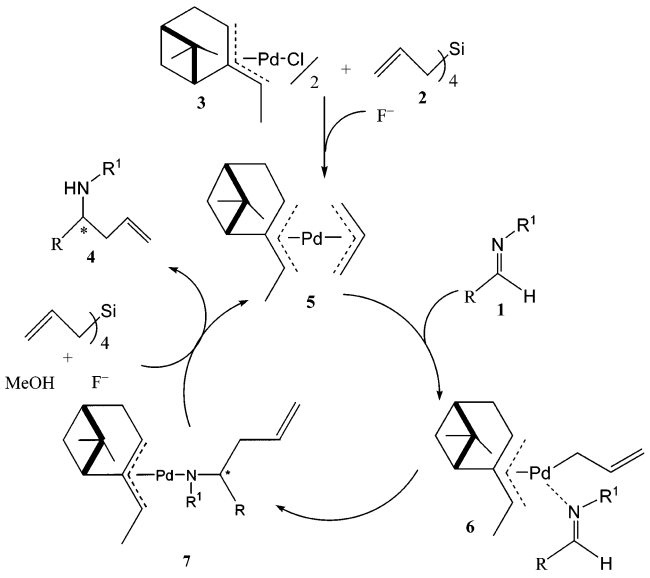
TABLE 2. Catalytic Asymmetric Allylation of Imines 1 with the Tetraallylsilane−TBAF−MeOH System, Using Catalyst 3[a]

entry	imine	R	R[1]	amine	time (h)	%yield[b]	%ee[c]
1	**1a**	Ph	$PhCH_2$	**4a**	14	86	91
2	**1b**	Ph	*o*-MeO-$C_6H_4CH_2$	**4b**	21	83	88
3	**1c**	Ph	*p*-MeO-$C_6H_4CH_2$	**4c**	19	83	90
4	**1d**	Ph	allyl	**4d**	19	83	84
5	**1e**	(*E*)-cinnamyl	$PhCH_2$	**4e**	20	86	74
6	**1f**	2-naphthyl	$PhCH_2$	**4f**	28	76	91
7	**1g**	2-naphthyl	*p*-MeO-$C_6H_4CH_2$	**4g**	28	78	90
8	**1h**	*p*-Me-C_6H_4	$PhCH_2$	**4h**	14	92	92
9	**1i**	*p*-MeO-C_6H_4	$PhCH_2$	**4i**	22	84	94
10	**1j**	*o*-MeO-C_6H_4	$PhCH_2$	**4j**	20	80	88
11	**1k**		$PhCH_2$	**4k**	15	88	90
12	**1l**		*p*-MeO-$C_6H_4CH_2$	**4l**	18	78	90
13	**1m**		$PhCH_2$	**4m**	22	89	89
14	**1n**	cyclohexyl	$PhCH_2$	**4n**	20	86	52
15	**1o**	2-furyl	$PhCH_2$	**4o**	18	89	76
16	**1p**		$PhCH_2$	**4p**	18	90	67
17	**1q**	*p*-MeO-C_6H_4	*p*-MeO-$C_6H_4CH_2$	**4q**	26	80	92
18	**1r**		Me	**4r**	36	68	55
19	**1s**		$PhCH_2$	**4s**	32	98	67

[a] All reactions were carried out with tetraallylsilane (1.2 equiv), TBAF (25 mol %), MeOH (1 equiv), catalyst **3** (5 mol %), in THF: hexane (1:2) at 0 °C for the specified time. [b] Yields of amine product by direct loading of reaction mixture onthe silica gel column (see Supporting Information for details). [c] Ee was determined by HPLC. For absolute configuration determination, see ref 2b.

dium complex **3** was studied for various imines to furnish the corresponding homoallylamines in high yields and good to excellent enantioselectivities as shown in Table 2. *N*-Benzylidenebenzylamine **1a** reacted in a shorter time, giving homoallylamine **4a** in good yield and 91% ee (Table 2, entry 1). Changing the *N*-substituent from benzyl to *o*- or *p*-methoxybenzyl gave similar results (Table 2, entries 2 and 3). *N*-Allyl-substituted imine **1d** reacted well to furnish *N*-allyl homoallylamine **4d** in 83% yield and 84% ee (Table 2, entry 4). Similarly *N*-cinnamylidenebenzylamine **1e** gave the corresponding homoallylamine **4e** in good yield and moderate enantioselectivity (Table 2, entry 5). *N*-2-Naphthylideneamine with benzyl (**1f**) or *p*-methoxybenzyl (**1g**) groups produced the corresponding homoallylamines **4f** and **4g** in good yields and 91% and 90% ee, respectively (Table 2, entries 6 and 7). *p*-Methylbenzylidenebenzylamine **1h** and *p*-methoxybenzylidenebenzylamine **1i** reacted in excellent yields and ee's of 92% and 94%, respectively (Table 2, entries 8 and 9). *o*-Methoxybenzylidenebenzylamine **1j** also reacted well to furnish the corresponding homoallylamine **4j** in 88% ee (Table 2, entry 10). In the piperonyl series (Table 2, entries 11−13) all three structurally different imines **1k**−**m** reacted well, giving homoallylamines **4k**−**m** in around 90% ee. *N*-Cyclohexylidene-, *N*-2-furylidene-, and *N*-2-thiophenenylidene-amines

SCHEME 1. Plausible Reaction Mechanism



(**1n**−**p**) reacted in good yields and moderate enantioselectivities (Table 2, entries 14−16). *p*-Methoxybenzylidene-*p*-methoxylbenzylamine **1q** furnished homoallylamine **4q** in 80% yield and excellent ee of 92% (Table 2, entry 17). The *N*-pyridyl-based imine with the *N*-methyl (**1r**) group was slow in reacting and furnished the corresponding homoallylamine **4r** in moderate yield and enantioselectivity (Table 2, entry 18). However *N*-benzyl imine **1s** reacted faster in comparison and gave an excellent yield of homoallylamine **4s** (98%) with moderate ee (Table 2, entry 19).

A plausible mechanism of this allylation reaction is shown in Scheme 1. Mechanistic studies of the Pd(II)-catalyzed reaction have revealed that bis-π-allylpalladium complex **5** is the reactive intermediate[9] for the catalytic cycle and reacts with imines as a nucleophile, although the ordinary π-allylpalladium complexes such as π-allylPdX (X = OAc and halides) act as electrophiles.[10] We have also shown that the bis-π-allylpalladium complex has an amphiphilic character.[11] Thus, in intermediate **5** one allyl group acts as a transferable group and the other nontransferable allyl group determines the stereocontrol of allylation. Thus, the transmetalation between **3** and tetraallylsilane **2** is triggered by fluoride anion, which activates the cleavage of the C−Si bond. In the absence of fluoride anion no reaction occurred. The key step for the asymmetric induction could be the coordination of imine **1** to bis-π-allylpalladium complex **5** to furnish **6**, and the subsequent allylation would proceed in a six-membered chair-like transition state to give **7**. The subsequent transmetalation of tetraallylsilane to palladium to regenerate **5** is triggered by fluoride anion and the protonation of **7** is assisted by methanol to give the product amine **4**. This would eventually lead to a shorter reaction rate.

Conclusions

In summary, we have demonstrated the first application of tetraallylsilane in asymmetric allylation of imines under catalytic, non-Lewis acid, essentially neutral, and very mild reaction conditions. The reaction is triggered by dual activation/promotion by TBAF and MeOH. We are now able to synthesize chiral homoallylamines in much shorter reaction time and high yields and enantioselectivities through an efficient, general, and reproducible allylation protocol for imines. Our quest continues toward the allylation of imines and aldehydes with substituted allylsilanes. We believe that this allylation protocol will find wide applicability in organic synthesis.

Supporting Information Available: Experimental details for catalyst preparation and separation and characterization data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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