Amine Synthesis

Asymmetric Synthesis of Diarylmethyl Amines by Rhodium-Catalyzed Asymmetric Addition of Aryl Titanium Reagents to Imines**

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Asymmetric synthesis of diarylmethyl amines has attracted growing attention owing to their importance in biological activity.[1] Among several methods for performing the asymmetric synthesis,[2,3] catalytic asymmetric addition of aryl metal reagents to imine derivatives seems to be most promising, provided that both high enantioselectivity and high catalytic activity are realized.[4] After our publication on the rhodium-catalyzed asymmetric addition of aryl stannanes to *N*-sulfonylimines,[5] two reports appeared on catalytic asymmetric arylation: 1) Bräse, Bolm, and co-workers described the addition of a phenylzinc reagent to masked *N*-formylimines in the presence of a chiral ketimine catalyst,[6] and 2) Tomioka illustrated the rhodium-catalyzed addition of aryl boroxines to *N*-tosylimines in which high enantioselectivity was observed for sterically tuned aryl imines.[7] Herein we report another rhodium-catalyzed asymmetric arylation in which the addition of aryl titanium reagents to sulfonylimines proceeds with high enantioselectivity under mild conditions (20 °C, 1 h) to give diarylmethyl amines with up to 96 % *ee*.

During our studies on rhodium-catalyzed asymmetric 1,4-additions to α,β-unsaturated ketones,[8] we found that the phenyltitanium reagent $PhTi(OiPr)_3$ is highly reactive toward transmetalation and forms a phenyl–rhodium bond. In the presence of a rhodium/(*S*)-binap catalyst in THF at 20 °C, the catalytic 1,4-addition gives titanium enolates as 1,4-addition products with high enantioselectivity.[9] Under similar reaction conditions (Scheme 1), the addition of $PhTi(OiPr)_3$[10] (**4a**) to *N*-tosylarylimine **1a**, which was prepared from 4-trifluoromethylbenzaldehyde and 4-toluenesulfonamide,[11] took place rapidly to give the tosylamide of diarylmethyl amine **5aa** after aqueous workup, unfortunately with only 28 % *ee* (Table 1, entry 1). The use of (*S*)-H_8-binap[12] and (*S*)-segphos[13] in place of (*S*)-binap[14] improved the enantioselectivity up to 43 % and 76 % *ee*, respectively (Table 1, entries 4 and 6). The relatively narrow dihedral angle of the biaryl bisphosphine ligand segphos[14] is considered to exert a positive influence on the enantioselectivity in the present

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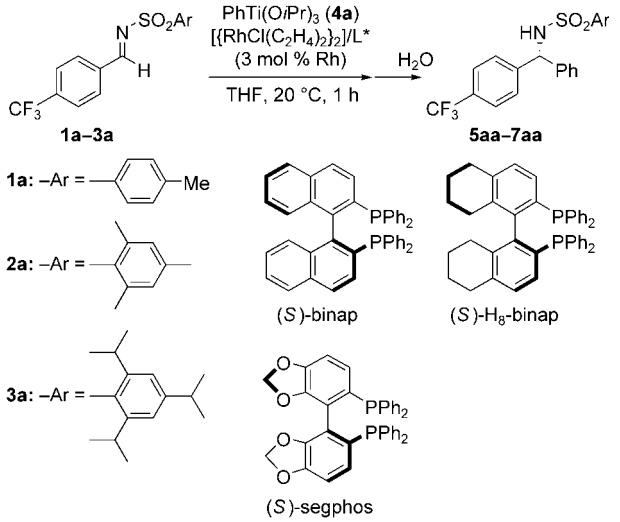
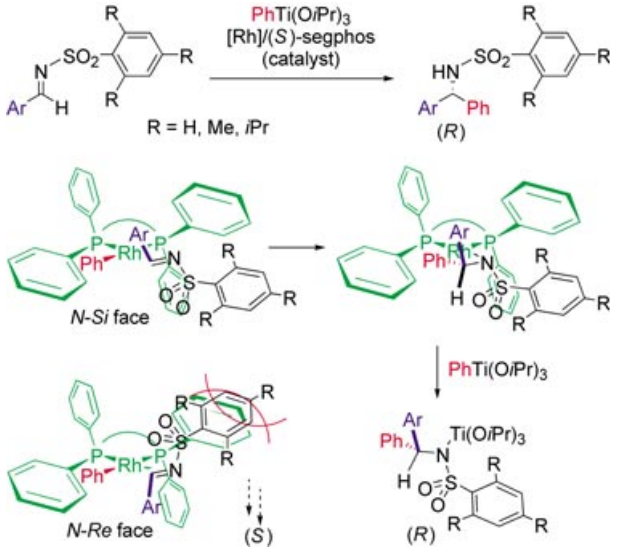


Scheme 1. Rhodium-catalyzed asymmetric arylation of imines **1a–3a** with $PhTi(OiPr)_3$ (**4a**).



Scheme 2. Stereochemical pathway in the catalytic asymmetric arylation of imines.

Table 1: Rhodium-catalyzed asymmetric arylation of imines **1a–3a** with $PhTi(OiPr)_3$ (**4a**).[a]

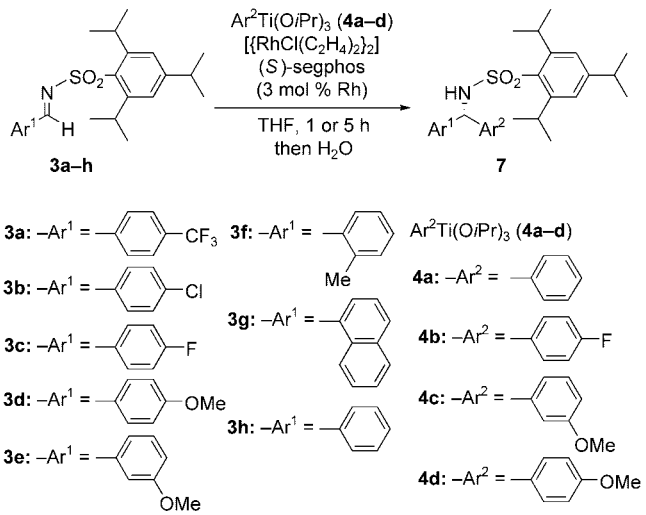
Entry	Imine	Ligand	Yield [%][b]	*ee* [%][c,d]
1	**1a**	(*S*)-binap	97 (**5aa**)	28 (*R*)
2	**2a**	(*S*)-binap	71 (**6aa**)	49 (*R*)
3	**3a**	(*S*)-binap	58 (**7aa**)	71 (*R*)
4	**1a**	(*S*)-H_8-binap	96 (**5aa**)	43 (*R*)
5	**3a**	(*S*)-H_8-binap	86 (**7aa**)	82 (*R*)
6	**1a**	(*S*)-segphos	99 (**5aa**)	76 (*R*)
7	**2a**	(*S*)-segphos	97 (**6aa**)	88 (*R*)
8	**3a**	(*S*)-segphos	98 (**7aa**)	93 (*R*)

[a] The reaction was carried out in THF at 20 °C for 1 h with **4a** (2 equiv) in the presence of the catalyst generated from $[\{RhCl(C_2H_4)_2\}_2]$ and a chiral phosphine ligand. [b] Yields of isolated amines (column chromatography: silica gel, hexane/EtOAc (2:1)). [c] Determined by HPLC analysis with a chiral stationary phase column (Chiralcel OD-H: hexane/2-propanol = 80:20 for **5aa** and **6aa**; hexane/2-propanol = 98:2 for **7aa**.). [d] The configurations of the amines were assigned by consideration of the stereochemical reaction pathway (see text).

asymmetric phenylation, although the enantioselectivity is still not satisfactory.

For the asymmetric 1,4-addition to α,β-unsaturated ketones,[15] esters,[16] and alkenylphosphonates[17] catalyzed by a rhodium complex coordinated with (*S*)-binap, we have proposed stereorecognition models that successfully rationalize the absolute configuration of the products. By applying this type of model to the present reaction of *N*-alkylidene sulfonamides,[18] it is evident that the enantioface of the imine is recognized by steric repulsions between one of the phenyl rings on the diphenylphosphino group and the aromatic ring on the arene sulfonamide (Scheme 2). Steric tuning of the arene sulfonamide moiety by introduction of sterically bulky groups onto the aromatic ring actually brought about enhancement of the enantioselectivity to an acceptable level. Thus, the asymmetric addition of phenyltitanium **4a** to mesitylenesulfonamide **2a** and triisopropylbenzenesulfonamide **3a** catalyzed by rhodium/(*S*)-binap gave the corresponding phenylation products **6aa** and **7aa** with 49 and 71% *ee*, respectively (Table 1, entries 2 and 3). The higher enantioselectivity in the asymmetric addition to triisopropylbenzenesulfonamide (**3a**) was also observed in the reaction catalyzed by the rhodium complexes of (*S*)-H_8-binap and (*S*)-segphos (Table 1, entries 5 and 8). The combination of (*S*)-segphos and triisopropylbenzenesulfonamide **3a** gave the diarylmethylamine (*R*)-**7aa** with 93% *ee* (Table 1, entry 8).

The present asymmetric phenylation with phenyltitanium **4a** catalyzed by rhodium/(*S*)-segphos was also successful for triisopropylbenzenesulfonamides of other aromatic imines **3**. The aromatic imines substituted with chloro (**3b**), fluoro (**3c**), and methoxy (**3d**) at the 4-position of the phenyl and the imines **3e–g** derived from 2-MeC_6H_4CHO, 3-$MeOC_6H_4CHO$, and 1-naphthaldehyde, respectively, gave the corresponding sulfonamides of diarylmethyl amines (*R*)-**7** in high yields (Scheme 3). The enantioselectivity ranged from 86 to 96% *ee*



Scheme 3. Asymmetric arylation of imines **3** with $ArTi(OiPr)_3$ (**4**) catalyzed by rhodium/(*S*)-segphos.

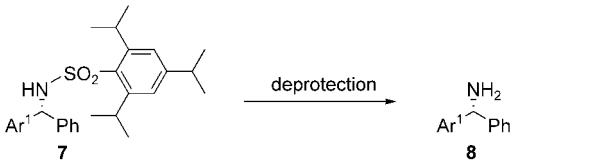
(Table 2, entries 2–7). The reaction of aryl titanium reagents **4b–d** (with the fluoro or methoxy group at the 3- or 4-position on the phenyl ring) also proceeded with high enantioselectivity (Table 2, entries 8–11). The reaction of imine **3h** with 4-fluorophenyltitanium **4b**, which is a reverse combination of the reaction of **3c** with **4a**, gave the *S* isomer of (4-fluorophenyl)(phenyl)methylamine **7ca** (93% *ee*) in quantitative yield (Table 2, entry 8). The reaction of 4-methoxyphenyltitanium **4d** with imines **3a** and **3b** proceeded as well to give diarylmethyl amines in which both aryl groups are substituted phenyls (Table 2, entries 10 and 11).

Table 2: Asymmetric arylation of imines **3** with $ArTi(OiPr)_3$ (**4**) catalyzed by rhodium/(*S*)-segphos.[a]

Entry	3	4	*T* [°C]	Yield [%][b]	*ee* [%][c, d]
1	**3a**	**4a**	20	98 (**7aa**)	93 (*R*)
2	**3b**	**4a**	20	95[e] (**7ba**)	94 (*R*)
3	**3c**	**4a**	30	99 (**7ca**)	92 (*R*)
4	**3d**	**4a**	40	98 (**7da**)	92 (*R*)
5	**3e**	**4a**	40	99 (**7ea**)	86 (*R*)
6[f]	**3f**	**4a**	20	99 (**7fa**)	89 (*R*)
7	**3g**	**4a**	30	99 (**7ga**)	96 (*R*)
8	**3h**	**4b**	20	96 (**7hb**)[g]	93 (*S*)
9[f]	**3h**	**4c**	40	86 (**7hc**)[h]	90 (*S*)
10	**3a**	**4d**	40	97 (**7ad**)	88 (*S*)
11	**3b**	**4d**	40	94 (**7bd**)	88 (*R*)

[a] The reaction was carried out in THF at the given temperature for 1 h with **4** (2 equiv) in the presence of the catalyst (3 mol%) generated from $[\{RhCl(C_2H_4)_2\}_2]$ and (*S*)-segphos. [b] Yields of isolated amines (column chromatography: silica gel, hexane/EtOAc (2:1)). [c] Determined by HPLC analysis with a chiral stationary phase column (Chiralcel OD-H: hexane/2-propanol = 98:2 for **7aa**, **7ba**, **7ca**, **7da**, **7hb**; hexane/2-propanol = 100:1 for **7ga**, **7ad**, **7bd**. Chiralcel AD-H: hexane/2-propanol = 98:2 for **7ea**, **7fa**). [d] The absolute configurations of **7ba**, **7da**, **7ga** were determined by comparison of the specific rotations of free amines **8** or their derivatives (see text). For other products, the configurations were assigned by consideration of the stereochemical reaction pathway. [e] The sulfonamide of (phenyl)(4-biphenylyl)methylamine was formed in 3% yield. [f] For 5 h. [g] Enantiomer of **7ca**. [h] Enantiomer of **7ea**.

The 2,4,6-triisopropylbenzenesulfonyl group[19] was removed from the diarylmethyl amines by standard methods for the deprotection of *p*-toluenesulfonamides (Scheme 4).[20] Treatment of **7da** ($Ar^1 = 4\text{-}MeOC_6H_4$) with lithium in liquid ammonia at −78 °C gave free amine **8da** in quantitative yield without loss of its enantiomeric purity. For **7ba** ($Ar^1 = 4\text{-}ClC_6H_4$) and **7ga** (Ar^1 = 1-naphthyl), the deprotection with lithium in ammonia was accompanied by reduction of the aryl groups to a considerable extent: $4\text{-}ClC_6H_4$ and 1-naphthyl gave phenyl and tetrahydronaphthyl, respectively. The deprotection was more selective with samarium iodide in HMPA/THF and RedAl in toluene for **7ba** and **7ga**, respectively.



For **7ba** ($Ar^1 = 4\text{-}ClC_6H_4$): SmI_2, HMPA, THF, reflux, 1 h: 53%
For **7da** ($Ar^1 = 4\text{-}MeOC_6H_4$): Li/NH_3 (liq), THF, −78 °C, 20 min: 100%
For **7ga** (Ar^1 = 1-naphthyl): RedAl, toluene, 80 °C, 5 h: 76%

Scheme 4. Deprotection of the sulfonamide.

In summary, the asymmetric synthesis of diarylmethyl amines was realized by rhodium-catalyzed asymmetric addition of aryl titanium reagents to *N*-alkylidene sulfonamides. A rational tuning of the arene sulfonamide moiety by introducing isopropyl groups onto the phenyl ring brought about high enantioselectivity (86–96% *ee*).

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