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Author(s)	Takizawa, Shinobu; Arteaga, Fernando Arteaga; Yoshida, Yasushi; Kodera, Junpei; Nagata, Yoshihiro; Sasai, Hiroaki
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ARTICLE TYPE

Vanadium-catalyzed enantioselective Friedel-Crafts-type reactions

Shinobu Takizawa, Fernando Arteaga Arteaga, Yasushi Yoshida, Junpei Kodera, Yoshihiro Nagata and Hiroaki Sasai*

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The vanadium-mediated enantioselective Friedel-Crafts (FC) type reactions have been established with the dinuclear vanadium complex (R_a,S,S,S)-**1a**. The vanadium complex promoted the FC type reaction of imines with 2-naphthols or indoles to give the corresponding adducts with high enantioselectivities.

Chiral vanadium complexes are known to be effective catalysts¹ for enantioselective and chemoselective oxidative reactions such as oxidation of sulfides to sulfoxides,^{1a,b} epoxidation of allylic alcohols,^{1c,d} coupling of 2-naphthols^{1e-g} and oxidation of α -hydroxy carbonyl compounds.² In the vanadium mediated homo-coupling of 2-naphthols³ and the oxidation of alcohols,² O₂ or air can be used as a co-oxidant to promote the catalytic reactions. In 2000, North and co-worker reported the first Lewis acid vanadium-salen catalysts for enantioselective cyanosilylation reaction.⁴ Although except for the asymmetric cyanation of carbonyl derivatives,^{1h,5} chiral vanadium catalysts which function as Lewis acid have been inadequately studied until now. Asymmetric carbon-carbon bond-forming processes using vanadium complexes have been a challenge for the construction of chiral complicated molecules.^{6,7} Herein we report vanadium catalyzed enantioselective Friedel-Crafts (FC) type reactions of *N*-tosyl imines with 2-naphthols or indoles. The dinuclear vanadium complex (R_a,S,S,S)-**1a** which works as a chiral Lewis acid to promote the FC type reactions with high enantiocontrol (Figure 1).

Asymmetric FC type reaction between phenols and aldimines is an important approach for the preparation of optically active amine-phenol motif (e.g. Betti base)^{8,9} which is frequently encountered in biologically active compounds¹⁰ and widely used in asymmetric transformations.¹¹ The first asymmetric FC

reaction of 2-naphthols and aldimines was presented by Hui^{8a} in 2010, using stoichiometric amount of a chiral zinc complex. In 2011, Wang^{8b} and Chimni^{8c} independently reported the catalytic enantioselective processes using 15-20 mol% of organocatalysts derived from *Cinchona* alkaloids.

We previously reported the chiral dinuclear vanadium complexes for enantioselective oxidative homo-coupling of 2-naphthols with dual activation mechanism.^{3n-p} We assumed that in the dinuclear vanadium catalyzed reaction, activation of 2-naphthol and imine by each vanadium metals in the chiral template could lead to make smooth hetero-coupling (Figure 2), giving Betti adduct with high enantioselectivity.

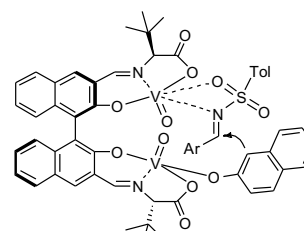


Figure 2 Plausible transition state for hetero-coupling of imine with 2-naphthol

To avoid a homo-coupling of 2-naphthol, the FC type reaction between 2-naphthol (**2a**) and 4-chlorophenyl *N*-tosylimine (**3a**) by vanadium catalysts was carried out at 10°C under N₂ atmosphere (Table 1).¹² Among the vanadium catalysts we tested, the dinuclear vanadium complexes (R_a,S,S,S)-**1a** possessing *t*Bu groups near to the active center, and (R_a,S,S,S)-**7** bearing H8-BINOL backbone exhibited high asymmetric induction ability (Table 1, Entries 1 and 4). The mononuclear vanadium complex (*S*)-**8** led to drastically decreasing enantiocontrol (Entry 5). The

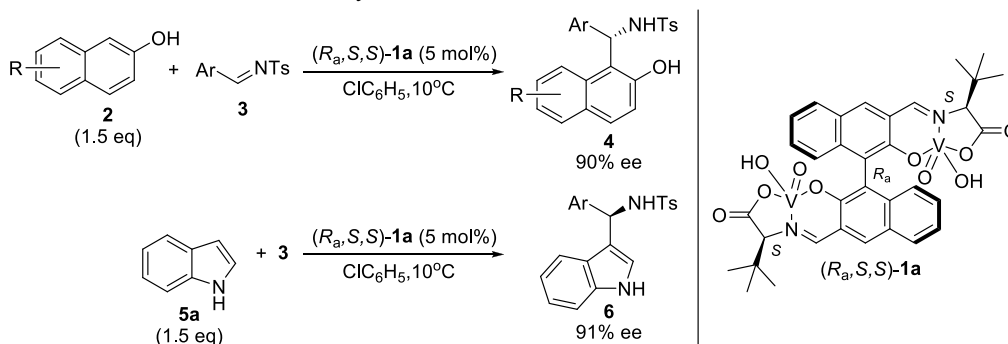
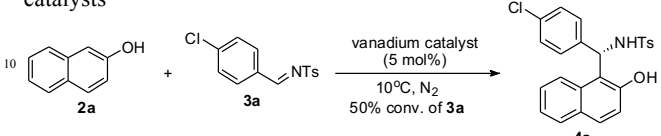


Figure 1 Vanadium-mediated enantioselective Friedel-Crafts (FC) type reactions of imines with 2-naphthols or indoles

optimal result (84% ee) was obtained when the reaction of **2a** (1.5 eq) with **3a** was performed in chlorobenzene (ClC₆H₅) at 10°C under N₂ atmosphere (Entry 12). After the 100% conversion of the imine **3a**, the product **4a** was obtained in 70% isolated yield with 85% ee (Table 2, Entry 1).

Table 1 Coupling reaction of **2a** with **3a** mediated by vanadium catalysts^a



Entry	Catalyst	Solvent	2a (eq)	% Ee ^b
1	(<i>R_a,S,S</i>)- 1a	Toluene	1.5	83
2	(<i>S_a,S,S</i>)- 1a	Toluene	1.5	63
3	(<i>R_a,S,S</i>)- 1b	Toluene	1.5	70
4	(<i>R_a,S,S</i>)- 7	Toluene	1.5	80
5	(<i>S</i>)- 8 ^c	Toluene	1.5	19
6	(<i>R_a,S,S</i>)- 9	Toluene	1.5	64
7	(<i>R_a,S,S</i>)- 10	Toluene	1.5	48
8	(<i>R_a,S,S</i>)- 1a	THF or MeCN	1.5	(no reaction)
9	(<i>R_a,S,S</i>)- 1a	CH ₂ Cl ₂	1.5	75
10	(<i>R_a,S,S</i>)- 1a	CCl ₄	1.5	30
11	(<i>R_a,S,S</i>)- 1a	ClC ₆ H ₅	1.0	82
12	(<i>R_a,S,S</i>)- 1a	ClC ₆ H ₅	1.5	84
13	(<i>R_a,S,S</i>)- 1a	ClC ₆ H ₅	2.0	80
14	(<i>R_a,S,S</i>)- 1a	ClC ₆ H ₅	3.0	70

^aTrace amount of BINOL was formed. ^bDetermined by chiral HPLC (Daicel Chiralpak IC). ^c10 mol % of (*S*)-**8** was used.

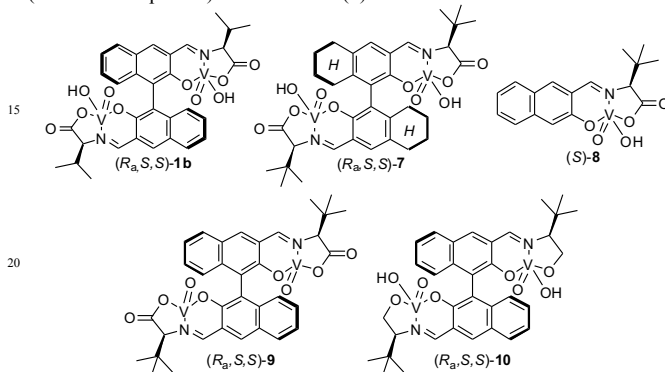


Table 2 Dinuclear vanadium complex (*R_a,S,S*)-**1a** catalyzed enantioselective Friedel-Crafts (FC) type reactions^a

Entry	2 or 5a	3 (Ar)	Time (d)	% Yield ^b	% Ee ^c
1	2a (R = H)	3a (4-Cl-C ₆ H ₄)	7	4a , 70	85
2	2a	3b (4-Br-C ₆ H ₄)	9	4b , 70	85
3	2a	3c (4-F-C ₆ H ₄)	8	4c , 70	76
4	2a	3d (4-Et-C ₆ H ₄)	9	4d , 67	81
5	2a	3e (4-MeO-C ₆ H ₄)	8	4e , 70	71
6	2a	3f (3-Cl-C ₆ H ₄)	6	4f , 70	89
7	2a	3g (2-Cl-C ₆ H ₄)	7	4g , 70	90
8	2a	3h (Ph)	8	4h , 70	71
9	2a	3i (2-thiophenyl)	6	4i , 80	60
10	2b (R = 6-Br)	3a	6	4j , 77	88
11	2c (R = 7-Me)	3a	6	4k , 82	61
12	5a	3a	4	6a , 80	76
13	5a	3b	3	6b , 80	76
14	5a	3j (2-Br-C ₆ H ₄)	9	6c , 77	91
15	5a	3k (2-naphthyl)	2	6d , 90	64

^aReaction conditions: **2** or **5** (0.15 mmol), **3** (0.10 mmol), catalyst (*R_a,S,S*)-**1a** (5 mol %), ClC₆H₅ (0.4 mL), 10°C, N₂. ^bIsolated yield. ^cDetermined by HPLC (Daicel Chiralpak IC for **4a**, **d**, **f**, **g**, **i**; Daicel Chiralpak AS-H for **4b**, **c**, **h**, **j**, **k**; Daicel Chiralpak AD-H for **4e**; Daicel Chiralcel OD for **6a**, **c**; Daicel Chiralcel OD-H for **6b**, **d**).

Under the optimal conditions, (*R_a,S,S*)-**1a** promoted the FC type reaction with high enantiocontrol for various substituted aromatic *N*-tosylimines with **2a** (Table 2). 2-Thiophenyl *N*-tosylimine (**3i**), 6-bromo-2-naphthol (**2b**) and 7-methyl-2-naphthol (**2c**) were suitable substrates (Entries 9-11). The dinuclear vanadium complex (*R_a,S,S*)-**1a** was also found to be effective for the FC type reactions of imines with indole **5a** (Entries 12-15). In the vanadium catalyzed FC reactions of **5a**, no bis-indole formation as a main side-reaction¹³ was observed at all. The highest enantiomeric excess value of product was obtained when the reaction of **5a** with 2-bromophenyl *N*-tosylimine (**3j**), affording the corresponding adduct **6c** with 91% ee (Entry 14). A non-substitution on indole nitrogen plays an important role in interaction with the chiral vanadium center leading to high asymmetric induction onto the product (Figure 3).

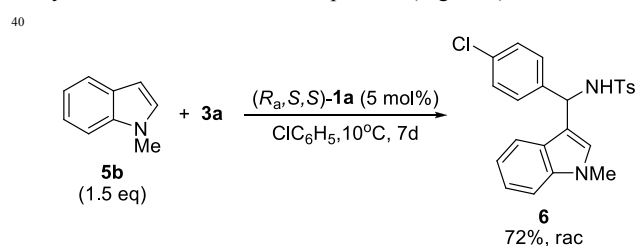


Figure 3 the FC type reaction of *N*-methyl indole (**5b**) with **3a**

In conclusion, we have discovered the first vanadium mediated enantioselective catalytic FC type reaction of *N*-tosyl imines with 2-naphthols or indoles. A wide variety of aryl aldimine substrates bearing either electron-withdrawing or electron-donating groups could be employed with 5 mol % of (*R_a,S,S*)-**1a** successfully.

Gaining insights into the exact active vanadium species V(V) or V(IV) on the FC reactions and application of the dinuclear vanadium complexes for developing new asymmetric FC type reactions are in progress.

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The Institute of Scientific and Industrial Research (ISIR), Osaka University, Mihogaoka, Ibaraki, Osaka 567-0047, Japan. E-mail: sasai@sanken.osaka-u.ac.jp; Fax: +81 6 6879 8465; Tel: +81 6 6879 8469

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