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Rhodium-Catalyzed Enantioselective Synthesis of β-Amino Alcohols via Desymmetrization of *gem*-Dimethyl Groups

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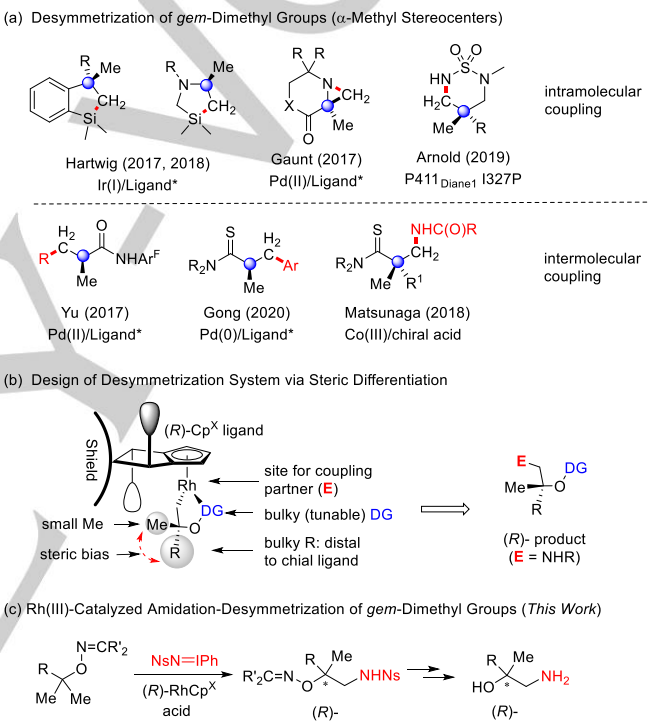
Dedicated to the 100th anniversary of Chemistry at Nankai University

Abstract: Desymmetrization of *gem*-dimethyl groups *en route* to the rhodium(III)-catalyzed enantioselective sp^3 C-H amidation is reported. Synthetically important β-amino alcohol derivatives were accessed in moderate to good yields and high enantioselectivity. The high enantioselectivity is enabled by an appropriate oxime directing group, sterically biased *gem*-groups in the C-H substrate, and high reactivity of the amidating reagent.

The methyl group is a magic partner in drug design and its presence may offer great advantage in improving medicinal properties such as half-life time, solubility, or binding affinity.[1] Synthetic methods to build X-Me (X = O, N, S, mostly) bonds are under great demand, especially when X represents a carbon atom.[2] While metal-catalyzed C-H activation has provided various approaches for construction of C-Me bonds,[1b] enantioselective construction of α-methyl stereocenter by catalytic C-H methylation remains underexploited, and, to our knowledge, direct C-Me coupling between electrophilic methylating reagent and prochiral C-H or enolate substrates has not been reported. Thus, alternative strategies to address this challenge have been developed.[3] Among the protocols, desymmetrization of *gem*-dimethyl groups has received increasing attention with the development of metal catalyzed C-H activation.[4] Following the intial report by Yu and coworkers,[4a] seminal studies on intramolecular[5-7] or more challenging intermolecular couplings[8-10] by desymmetrization strategy have been recently disclosed by Hartwig,[5] Gaunt,[6] Arnold,[7] Yu,[8] Matsunaga,[9] and Gong[10] (Scheme 1a), with metal catalysis being dominating. Despite the progress, desymmetrization of *gem*-dimethyl groups seems limited in reaction patterns or enantioselectivity, and further studies remain necessary.

β-Amino alcohols represents an important structural motif in a diverse array of natural products and pharmaceuticals.[11] They are also useful chiral auxiliaries in asymmetric catalysis and building blocks for valuable products.[12] In 2014, the Chang group reported racemic synthesis of β-amino alcohols via Ir(III)-catalyzed C-H amidation of alcohol derivatives containing an *N*-directing group.[13a] On the other hand, Chang,[13b] Cramer,[14] He,[15] Shi,[16] Matsunaga,[17] and our group[18] recently reported enantioselective desymmetrization of arenes in annulation,



Scheme 1. Desymmetrization of *gem*-Dimethyl Groups.

arylation, and amidation reactions, which occurred via enantiodetermining C(aryl)-H activation catalyzed by rhodium and iridium complexes.[19] Meanwhile, desymmetrization of the coupling partner has also been reported.[20] However, although Rh/Ir-catalyzed enantioselective sp^3 C-H functionalization[21] have been realized, desymmetrization of *gem*-dimethyl groups remains largely underexplored.[22] We aimed to adopt chiral Cp^XRh^{III}-catalyzed desymmetrization-amidation of *gem*-dimethyl groups for synthesis of chiral β-amino alcohols. However, enantiotopic discrimination of *gem*-dimethyl groups seems challenging, and discrimination of the methyl groups in a *i*Pr is perticularly challenging, as described in Yu's pinoneering work.[8] Following C-H activation (Scheme 1b), the R and the methyl groups are distal to the metal center, which poses challenges in chiral discrimination.[4a,b,8] The solution to this system probably boils down to identification of a suitable directing group (DG) that serves to dictate the orientation of the reacting methyl group toward C-H activation. We reasoned that a bulky DG offers

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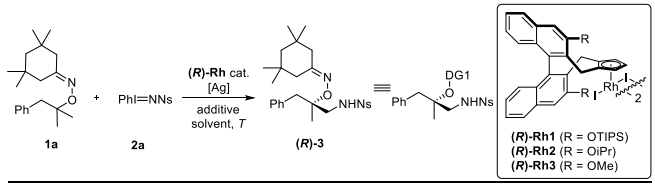
steric repulsion to push the neighboring R and spectatoring Me groups toward the steric group in the chiral ligand. Conseququently, the steric bias between the Me and R group allowed for discrimination of enantiotopic methyl groups so that the smaller (onlooking) Me group is disposed closer to the blocking group. We now report Cp^XRh^{III}-catalyzed desymmetrization-amidation of *gem*-dimethyl groups for synthesis of functionalized chiral amino alcohols containing a *α*-methyl stereocenter (Scheme 1c).

Table 1. Optimization Studies.[a]

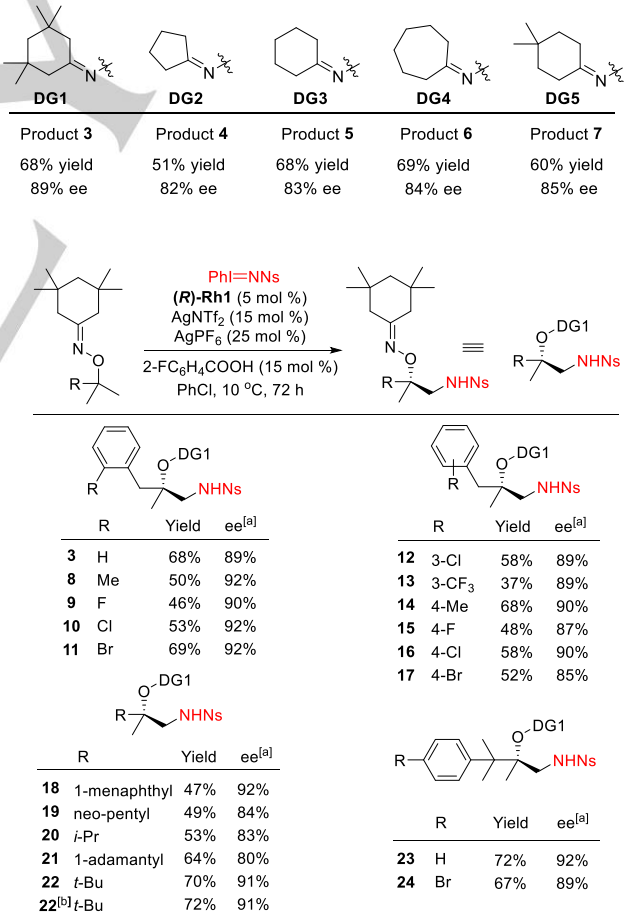


entry	cat.	[Ag] (x mol%)	additive (y mol%)	solvent	yield [%][b]	ee [%]
1[c]	**(*R*)-Rh1**	$AgSbF_6$ (20)	NaOPiv (30)	PhCl	35	80
2[c]	**(*R*)-Rh2**	$AgSbF_6$ (20)	NaOPiv (30)	PhCl	16	61
3[c]	**(*R*)-Rh3**	$AgSbF_6$ (20)	NaOPiv (30)	PhCl	15	59
4[d]	**(*R*)-Rh1**	$AgSbF_6$ (20)	NaOPiv (30)	PhCl	n.d.	-
5[e]	**(*R*)-Rh1**	$AgSbF_6$ (20)	NaOPiv (30)	PhCl	< 5	11
6	**(*R*)-Rh1**	$AgSbF_6$ (20)	AcOH (30)	PhCl	32	75
7	**(*R*)-Rh1**	$AgSbF_6$ (20)	PivOH (30)	PhCl	32	65
8	**(*R*)-Rh1**	$AgSbF_6$ (20)	PhCOOH (30)	PhCl	40	75
9	**(*R*)-Rh1**	$AgSbF_6$ (20)	2-FC_6H_4COOH (30)	PhCl	46	79
10	**(*R*)-Rh1**	$AgSbF_6$ (20)	2-FC_6H_4COOH (15)	PhCl	25	86
11[f]	**(*R*)-Rh1**	$AgSbF_6$ (20)	2-FC_6H_4COOH (15)	PhCl	36	86
12[f]	**(*R*)-Rh1**	$AgPF_6$ (20)	2-FC_6H_4COOH (15)	PhCl	41	85
13[f]	**(*R*)-Rh1**	$AgNTf_2$ (20)	2-FC_6H_4COOH (15)	PhCl	11	92
14[f]	**(*R*)-Rh1**	$AgPF_6$ (25) $AgNTf_2$ (15)	2-FC_6H_4COOH (15)	PhCl	40	89
15[f,g]	**(*R*)-Rh1**	$AgPF_6$ (25) $AgNTf_2$ (15)	2-FC_6H_4COOH (15)	PhCl	68	89

[a]Reaction Conditions: **1a** (0.2 mmol), **2a** or in situ generated **2a** from $NsNH_2$ and $PhI(OAc)_2$ (0.1 mmol), **(*R*)-Rh** (5 mol%), [Ag] (x mol%), additive (y mol%), solvent (2 mL), under Ar for 72 h at 0 °C. [b]isolated yield. [c]in situ generated **2a** was used. [d]TsN_3 was used instead of **2a**. [e]3-(*p*-tolyl)-1,4,2-dioxazol-5-one was used instead of **2a.** [f]**1a**:**2a** = 2:1. [g]10 °C. Ns = 4-$NO_2(C_6H_4)SO_2$. Tf = CF_3SO_2.

Oxime ether **1a** bearing a relatively bulky **DG1** was chosen as a model substrate (Table 1). Its coupling with *in situ* generated iodonium imide[23] **1b** using $Cp^XRh(III)/AgSbF_6$ catalyst in the presence of NaOPiv afforded the desired product **3** in a low yield with 80% ee (entry 1). Other $Cp^XRh(III)$ catalysts all gave inferior yield and enantioselectivity (entries 2 and 3). Other *N*-sources[24] were also screened, and no or traces of corresponding product was detected when TsN_3 or dioxazolone[24a] was used (entries 4 and 5). Carboxylic acid plays an important role in C-H activation or desymmetrization reactions.[14b,18,25] However, in situ generation of **2a** is accompanied by two equivalents of HOAc that may override the extraneous acid. Thus, pre-formed **2a** was used instead. It was found that 2-fluorobenzoic acid (FC_6H_4COOH) was optimal, giving **3** in 46% yield and 79% ee (entries 6-9). Decreasing the amount of 2-FC_6H_4COOH slightly improved the enantioselectivity (entry 10). By adjusting the ratio of substrates, higher yield was achieved (entry 11). Silver salts were next screened, and the use of $AgNTf_2$ gave decreased yield but high ee (entries 12 and 13). Employment of mixed silver salts ($AgPF_6$ and $AgNTf_2$) at a higher reaction temperature finally afforded the product in 68% yield and 89% ee (entry 15). Besides, DGs derived from other cyclohexanones, cyclopentanones, and cycloheptanones were examined, which all gave lower enantioselectivities (Table 2, products **4**-**7** with 80-85% ee), indicating that the ring size and steric effects are crucial in enantioselective control.

Table 2. Effects of Directing Groups.



	R	Yield	ee[a]
3	H	68%	89%
8	Me	50%	92%
9	F	46%	90%
10	Cl	53%	92%
11	Br	69%	92%

	R	Yield	ee[a]
12	3-Cl	58%	89%
13	3-CF_3	37%	89%
14	4-Me	68%	90%
15	4-F	48%	87%
16	4-Cl	58%	90%
17	4-Br	52%	85%

	R	Yield	ee[a]
18	1-menaphthyl	47%	92%
19	neo-pentyl	49%	84%
20	*i*-Pr	53%	83%
21	1-adamantyl	64%	80%
22	*t*-Bu	70%	91%
22[b]	*t*-Bu	72%	91%

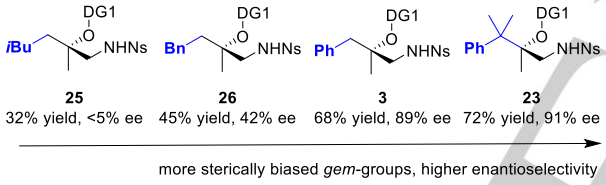
	R	Yield	ee[a]
23	H	72%	92%
24	Br	67%	89%

Scheme 2. Scope of Oxime Ethers. [a] Reaction Conditions: **1** (0.2 mmol), **2a** (0.1 mmol), **(*R*)-Rh1** (5 mol%), $AgPF_6$ (25 mol%), $AgNTf_2$ (15 mol%), 2-

FC_6H_4COOH (15 mol%), PhCl (2 mL), under Ar for 72 h at 10 °C [b] 0.5 mmol scale.

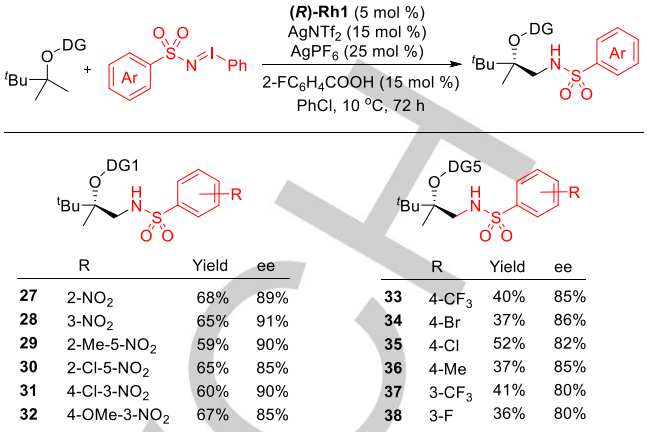
The scope of the oxime ethers was examined under the optimal conditions. Introduction of various substituents into the *ortho*, *meta*, and *para* positions of the phenyl ring in the benzyl group afforded *β*-Amino alcohol derivatives (**8**-**17**) in acceptable yield (37-69%) and high enatioselectivity (84-92% ee). Among these results, the presence of *ortho* substituent tends to consistently give higher ee (products **8**-**11**), likely due to steric effect. The absolute configuration of product (*R*)-**11** has been determined by X-ray crystallography (CCDC 2035597). Analogously, oxime ether bearing a menaphthyl group coupled in 92% ee (**18**). Sencondary alkyl substituents such as *neo*-pentyl and *i*-Pr groups only gave moderate ee (**19** and **20**), indicating importance of both electronic and steric effects. The presence of tertiary alkyl group generally led to good yield and high ee (**22**-**24**). The scale-up synthesis of **22** was also conducted, giving 72% yield with 91% ee. However, somewhat lower ee was obtained when 1-Ad was introduced (**21**).

Representative substrates were allowed to react with **2a** to showcase the effect of steric bias on the reaction enantioselectivity. As shown in Scheme 3, almost racemic product was achieved when smaller R groups were introduced (**25**). The introduction of a bulkier R group led to higher enantioselectivity (**26**, **3** and **23**).



Scheme 3. Effects of the Steric Bias in the Substrate.

The scope of the amidating reagent was next investigated (Scheme 4). Iodonium imides bearing nitro group at different positions gave the corresponding products in good yield and high ee (**27** and **28**), and nitro-containing di-substituted iodonium imides were also tolerated (products **29**-**32**). When other substituents such as CF_3 and halogens were introduced, the reaction turned out to be very sluggish. According to our initial screening studies, **DG5** may also serve as a promising DG (product **7,** 60% yield and 85% ee in Table 2). Thus, we turned to oxime ether substrates bearing **DG5** for further scope studies (**33-38**). The less bulky **DG5** increased the reaction efficiency and the corresponding products **33-38** were obtained in 36-52% yield with 80-86% ee.

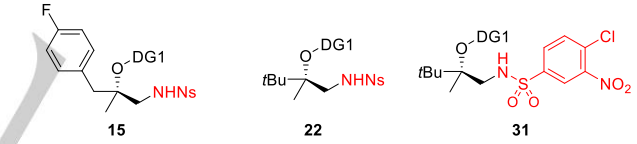


	R	Yield	ee
27	2-NO_2	68%	89%
28	3-NO_2	65%	91%
29	2-Me-5-NO_2	59%	90%
30	2-Cl-5-NO_2	65%	85%
31	4-Cl-3-NO_2	60%	90%
32	4-OMe-3-NO_2	67%	85%

	R	Yield	ee
33	4-CF_3	40%	85%
34	4-Br	37%	86%
35	4-Cl	52%	82%
36	4-Me	37%	85%
37	3-CF_3	41%	80%
38	3-F	36%	80%

Scheme 4. The Scope of Iodonium Imides (See Scheme 2 and Supporting Information for reaction conditions).

The utility of this protocol was next identified by the preliminary bioactivity study and synthetic derivatization. Considering the good bioactivities of the melarcules containing *β*-amino alcohol unit,[11] the introducton of methyl group may aslo give positive results. Thus, representative coupled products were tested toward REC-1 and Ramos cells, giving the 50% inhibitory concentration (IC_{50}) of cell death at micromolar or nanomolar level (Scheme 5, see SI for more information). Subsequent modification and optimization of the structure may afford a new class of anticancer precursors.



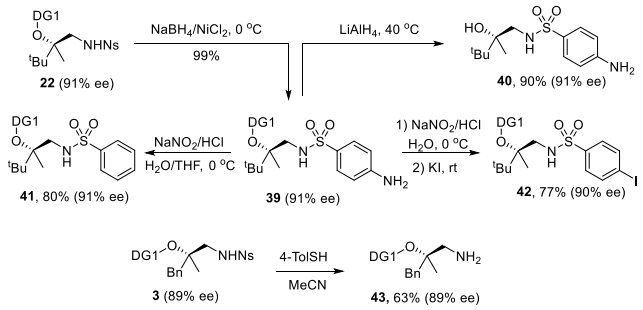
IC_{50} = 3.64 μM (REC-1 cell)
IC_{50} = 138 nM (Ramos cell)

3.72 μM (REC-1 cell)
1.66 μM (Ramos cell)

877 nM (REC-1 cell)
634 nM (Ramos cell)

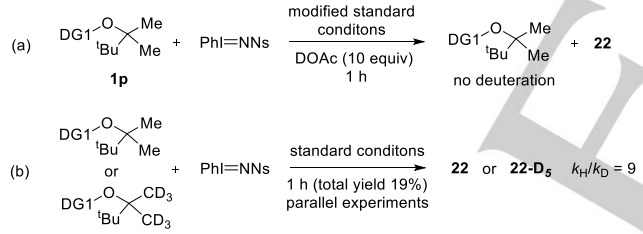
Scheme 5. IC_{50} of Selected Compounds toward REC-1 and Ramos cells.

Derivatizations of selected products were conducted to showcase the synthetic utility of this coupling system (Scheme 6). Chemoselective reduction of compound **22** gave product **39** in nearly quantitative yield. Reductive O-N cleavage of **22** led to removal of the DG in high yield (**40**). The presence of an amino group allowed further transformations to an aryl iodide (**42**) or deamination product (**41**) *via* diazonium intermediates**.** Removal of the Ns group in **3** gave product **43** in good yield.



Scheme 6. Derivatizations of the products.

We next conducted H/D exchange experiments by introducing 10 equivalents of AcOD under the standard conditions. No deuteration was detected either in the recovered substrate or the corresponding product **22**, indicating irreversibility of the methyl C-H activation (Scheme 7a). Parallel reactions were conducted using **1p** and **1p-*d*$_6$** to determine the kinetic isotope effect (KIE). The large KIE value of 9.0 suggests that cleavage of the methyl C−H bond is involved in the turnover-limiting step (Scheme 7b). Thus, the catalytic cycle involves DG- and acid-assisted stereodetermining C-H activation to give a rhodacycle in a diastereoselective fashion with the Me disposed closer to the blocking group (Scheme 1b). Subsequent Rh(V)-nitrene formation and migratory insertion into the nitrene is followed by protonolysis to give the amidation product in (*R*) selectivity.



Scheme 7. Mechanistic Studies

In summary, we demonstrated herein chiral Cp^{X}Rh^{III}-catalyzed enantioselective C-H activation-amidation of *gem*-dimethyl groups. The system is applicable to a decent scope of substrates, leading to functionalized *α*-methyl-*β*-amino alcohols in moderate to good yield and generally high enantioselectivity. The high enantioselectivity is ascribed to employment of a suitable oxime directing group, sterically biased groups in the C-H substrate, and high reactivity of the amidating reagents. Given the importance of *α*-methyl stereocenter and the utility of *β*-amino alcohols, this protocol may find applications in synthetic and medicinal chemistry.

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Conflict of interest

The authors declare no competing financial interest.

Keywords: rhodium • desymmetrization •*α*-methyl stereocenter •*β*-amino alcohol • amidation

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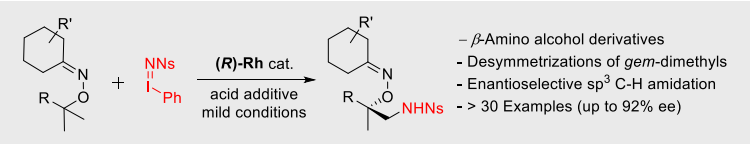

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Rhodium-Catalyzed Enantioselective Synthesis of *β*-Amino Alcohols via Desymmetrization of *gem*-Dimethyl Groups

Chiral Rh(III)-catalyzed enantioselective methyl C-H amidation via desymmetrization of *gem*-dimethyl groups afforded functionalized *α*-methyl-*β*-amino alcohols in high enatioselectivity (> 30 examples, up to 92% ee). The high enantioselectivity is ascribed to judicious choice of an oxime directing groups, sterically biased *gem*-groups in the C-H substrate, and high reactivity of the iodonium imide reagents.