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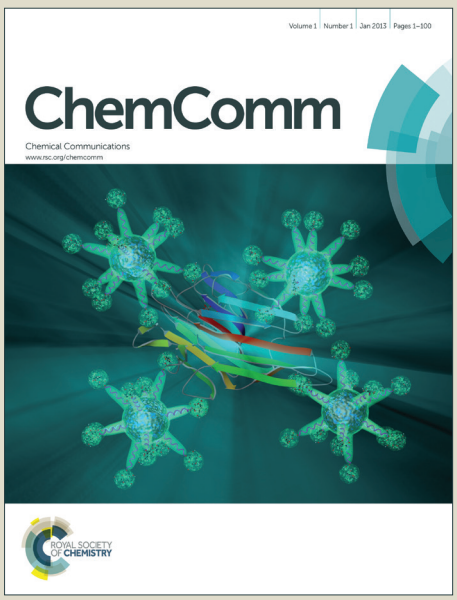

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Synthesis of 1,2-Amino Alcohols via Catalytic C–H Amidation of sp^3 Methyl C–H Bonds

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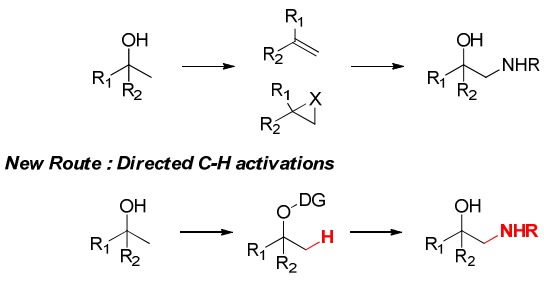
Herein a new synthetic route to 1,2-amino alcohols is presented by using C–H amidation of sp^3 methyl C–H bonds as a key step. Readily available alcohols were employed as starting materials after converting them to removable ketoxime chelating groups. Iridium catalyst was found to be effective for the C–H amidation, and LAH reduction was then used to furnish β-amino alcohol products.

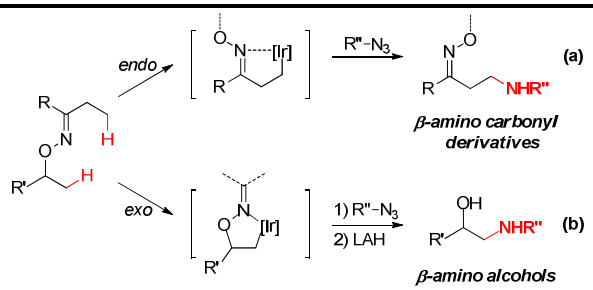
1,2-Amino alcohols (β-amino alcohols) are a versatile structural motif widely present in natural and unnatural products.[1] In applications such as medicine, materials, and total synthesis, β-amino alcohols play a pivotal role as a building unit. Given their importance, extensive efforts have been made towards the synthesis of 1,2-amino alcohols including (i) reduction/addition of carbonyl and imine compounds;[2] (ii) ring opening of epoxides/aziridines with suitable nucleophiles;[3] or (iii) olefin aminohydroxylation.[4] Direct transformation of C–H bonds has been an intensive recent research focus,[5,6] thus leading to a range of selective and straightforward transformations of readily available compounds to value-added products. In this regard, the direct C–H functionalization towards *intermolecular* synthesis of 1,2-amino alcohols is highly attractive since the presently available methods are rather limited mainly to an intramolecular C–H amidations of carbamates or sulfamates.[7]



Scheme 1. Synthetic Routes to β-Amino Alcohols from Alcohols

Based on our expedition in the direct C–H functionalization,[8] we have now established a synthetic protocol to furnish β-amino alcohols utilizing the sp^3 C–H bond amidation as a key step. Iridium catalytic system was optimized for the intermolecular amidation of chelation group-masked alcohols with azides as an amino source under mild conditions, thus avoiding functional group manipulations as in the case of conventional approaches (Scheme 1). The present route allows for the facile generation of an amino alcohol library by virtue of employing readily available alcohols and azides.

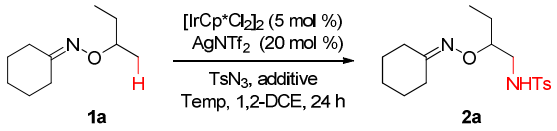
Recently, we have developed a Cp*Ir(III)-based catalytic system enabling the transformation of sp^3 methyl C–H bonds to amides.[9] In the presence of a ketoxime directing group, the catalyst selectively activates methyl C–H bonds which could form a five-membered iridacycle (Scheme 2). Based on this approach, a C=N *endo*-cyclic pathway was proved to work leading to β-amino carbonyls (Scheme 2a). At the same time, we also explored an *exo*-directing mode to afford 1,2-amino alcohols (Scheme 2b).[10]



Scheme 2. Ketoxime-Directed sp^3 C–H Amidation

To explore the Ir-catalyzed amidation of alcohol derivatives, a ketoxime of isobutanol (**1a**) was prepared to test as a model substrate (Table 1). A cationic Cp*Ir(III) species generated *in situ* from $[IrCp^*Cl_2]_2$ and $AgNTf_2$ displayed notable catalytic activity in the presence of acetate ions (entries 1–6). Whereas conversion was low without an acetate additive, cesium or silver acetate showed better performance over lithium, sodium, or copper(II) salts. With the use of *para*-toluenesulfonyl azide (TsN_3) in 2.0 equiv, the addition of catalytic amount of CsOAc (10 mol%) resulted in the most pronounced additive effects when compared to other salts (entries 7–8). While the amidation proceeded with highest efficiency at 60 °C, product yields were decreased at either lower or higher temperatures (entries 8–10).

Table 1. Optimization of the Reaction Conditions[a]

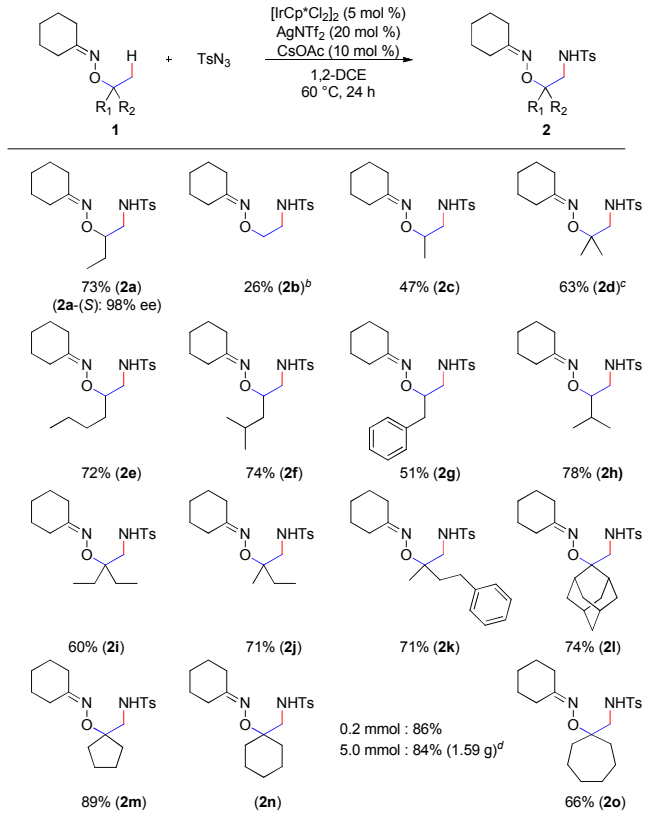


entry	TsN_3 (equiv)	additive	temp (°C)	yield (%)[b]
1	1.5	-	60	28
2	1.5	AgOAc	60	78
3	1.5	CsOAc	60	78
4	1.5	NaOAc	60	58
5	1.5	LiOAc	60	62
6	1.5	$Cu(OAc)_2$	60	52
7	2.0	AgOAc	60	78
8	**2.0**	**CsOAc**	**60**	**84**
9	2.0	CsOAc	40	10
10	2.0	CsOAc	80	60

[a] **1a** (0.2 mmol) and additive (10 mol %) in 1,2-dichloroethane (0.5 mL). [b] ^{1}H-NMR yield (1,1,2,2-tetrachloroethane: internal standard).

With the optimized conditions in hand, the scope of substrates was next investigated. Assorted kinds of alcohols after converting to cyclohexane ketoximes were found to readily react with TsN_3 giving rise to the corresponding β-amino alcohols (Table 2). As the alcohol moiety was varied from primary to tertiary, the amidation was more facile leading to higher product yields (**2b–d**).

Table 2. Substrate Scope of Ketoximes[a]



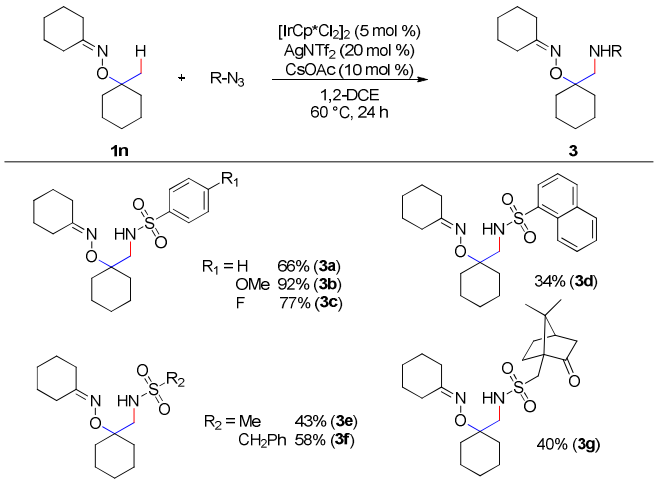
[a] **1** (0.2 mmol) and TsN_3 (0.4 mmol) in 1,2-DCE (0.5 mL): isolated yields. [b] ^{1}H-NMR yield (internal standard: 1,1,2,2-tetrachloroethane). [c] TsN_3 (1.5 equiv) was used and diamidated product was obtained (12%). [d] **1n** (5.0 mmol) and TsN_3 (10 mmol) in 1,2-DCE (7.5 mL).

On the basis of this result, a series of substrates derived from secondary or tertiary alcohols were subjected to the reaction conditions, and synthetically acceptable product yields were obtained from most reactions examined. Significantly, substrates derived from both acyclic (**2e–k**) and cyclic alcohols (**2l–o**) were successfully applied to the amidation procedure.

Several features of the present amidation process are especially noteworthy as follows. (i) The amidation occurred exclusively at the methyl C–H bonds in the presence of methylene group, and even the benzylic methylene moiety did not participate in the amidation (**2g**). (ii) Only a five-membered iridacycle pathway was selectively allowed, and amidation involving six- (e.g. **2a** and **2h–j**) or higher-membered sp^3 metallacycle intermediates were not observed (**2e–f**) although the same Cp*Ir(III) catalyst system was known to activate sp^2 C–H bonds through both five- and six-membered iridacycles.[11,12] (iii) Monoamidation occurred highly selectively even with substrates bearing multiple methyl groups (**2c** and **2j–k**) although a bis-amidation also took place as minor (12%) in addition to the mono-amidation (63%) when a substrate derived from *tert*-butyl alcohol was reacted (**1d**). Amidation of an optically enriched substrate proceeded without erosion of enantiomeric excess (**2a-*S***). In addition, a gram scale reaction was also smooth without difficulty (**2n**).

Next, a focus was shifted to the scope of organic azides. The optimized amidation conditions were readily applied to various sulfonyl azides as the coupling partner in reaction with **1n** (Table 3). While electronic variation of arenesulfonyl azides did not deteriorate the reaction efficiency (**3a–c**), amidation with 1-naphthalenesulfonyl azide resulted in rather lower product yield (**3d**). On the other hand, the amidation efficiency in reaction with alkanesulfonyl azides was observed to be relatively lower (**3e–g**) when compared to that with arenesulfonyl analogues.

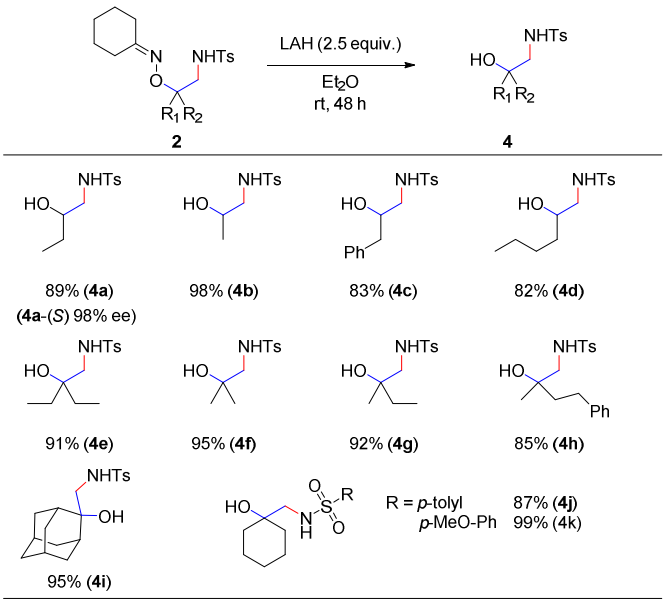
Table 3. Substrate Scope of Organic Azides[a]



[a] **1n** (0.2 mmol) and organic azides (0.4 mmol) in 0.5 mL of 1,2-DCE: isolated yields.

At last, it was demonstrated that the ketoxime directing group, installed for the iridium-catalyzed C–H bond activation, could be readily removed to afford β-amino alcohols (Table 4). Upon screening of various plausible conditions,[13] we found that lithium aluminium hydride (LAH in anhydrous ether solution, 2.5 equiv) cleanly removed the ketoxime directing group at room temperature in excellent yields to furnish the corresponding β-hydroxy sulfonamides. It is noteworthy that this C–H amidation/N–O bond cleavage protocol is one of a few examples of highly regioselective production of 1-amino-2-alcohols.[14]

Table 4. Removal of Ketoxime Group to Give 1, 2-Amino Alcohols



In conclusion, we have developed a highly efficient and selective preparative procedure for 1,2-amino alcohols. The key step is the Ir-catalyzed direct C–H amidation of sp^3 methyl C–H bonds using organic azides as the amino source under mild conditions. Various types of alcohols could readily be employed for the present approach after converting them to removable directing groups.

Notes and references

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† Electronic Supplementary Information (ESI) available : Experimental details and copies of spectra. See DOI: 10.1039/c000000x/

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