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Chemo- and Regioselective Direct Functional Group Installation through Catalytic Hydroxy Group Selective Conjugate Addition of Amino Alcohols to α,β-Unsaturated Sulfonyl Compounds

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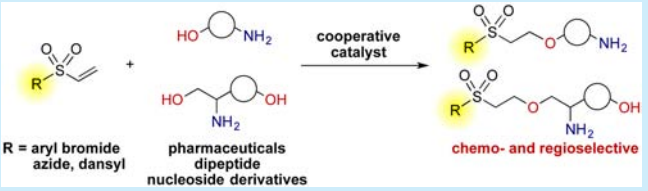
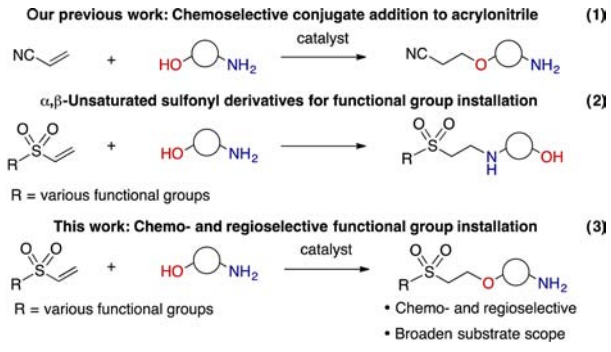
Supporting Information

ABSTRACT: A chemoselective functional group installation through catalytic hydroxy group selective conjugate addition of amino alcohols to a variety of functionalized α,β-unsaturated sulfonyl derivatives was developed. Azide group installation for click chemistry and facile fluorescent labeling onto the less reactive hydroxy group demonstrated the synthetic utility of the present chemoselective catalysis. Moreover, chemo- and regioselective reaction of an unprotected amino diol was achieved for the first time.



Protecting group free transformation of the molecules is a primary goal in synthetic chemistry.[1] One method to achieve this aim is functional group selective synthesis (chemoselective synthesis).[2] Although several chemoselective reactions that generally rely on innate reactivity have been reported, catalyst-controlled reversal of innate reactivity has remained a formidable challenge. We recently developed a catalytic chemoselective conjugate addition of amino alcohols to α,β-unsaturated nitriles in which an innately less reactive hydroxy group was selectively functionalized (eq 1).[3] An



advantageous feature of this chemoselective catalysis was the wide substrate scope, including β-amino alcohols, which could not be applied to previously reported catalyst-controlled chemoselective reactions.[4] Although the nitrile functionality of the hydroxy group adduct can be transformed into versatile functionalities, the protocol requires a multistep sequence, and direct catalytic installation of various functional groups onto less nucleophilic hydroxy groups of unprotected amino alcohol has never been achieved.

We focused on α,β-unsaturated sulfonyl derivatives for direct functional group installation.[5] α,β-Unsaturated sulfonyl derivatives were used as labeling reagents due to their highly electrophilic nature. Precedents, however, were limited to the attachment of these derivatives on innately more nucleophilic amino or thiol groups, even in the presence of a hydroxy group (eq 2).[6] On the basis of our previous report, we envisioned that a cooperative catalyst comprising soft Lewis acids and hard Brønsted bases would enable the chemoselective deprotonative activation of hard hydroxy groups, allowing for chemoselective functional group installation with α,β-unsaturated sulfonyl derivatives (eq 3).

We began our investigation using L-phenylalaninol (**2a**) as a model substrate with unsubstituted phenyl vinyl sulfone (**1a**), which has never been utilized for catalytic conjugate addition of hydroxy groups due to its highly reactive nature to polymerize under basic conditions.[7] In the absence of a catalyst, amino group adduct **4aa** was exclusively formed in 64% yield (Table 1, entry 1). The reaction was performed at a lower temperature to suppress polymerization. Hydroxy group adduct **3aa** was formed in high yield under a copper/base cooperative catalyst system (entries 2 and 3).[8] We then turned our attention to other Lewis acids. Systematic screening of metal salts revealed that silver(I) acetate afforded the desired product in slightly better yield and high chemoselectivity (entry 4). Combining silver(I) acetate with other Brønsted bases produced the same catalytic activity, except for NaHMDS (entries 5−7). AgHMDS functioned as a comparable catalyst (entry 8). Both the silver(I) and the Brønsted base were essential for obtaining **3aa** in high yield with high chemoselectivity (entries 9 and 10). As expected, Brønsted base catalysis using KHMDS gave a complex mixture due to the competitive polymerization of **1a**, although conjugate addition of alcohol was promoted.[9,10]

Having determined the optimal conditions (Table 1, entry 7), we next investigated the scope of sulfonyl derivatives that

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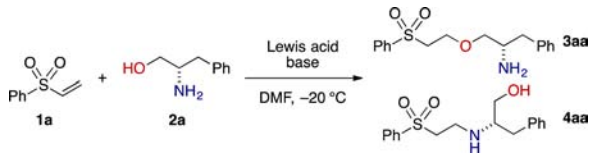
Table 1. Conditions Optimization[a]

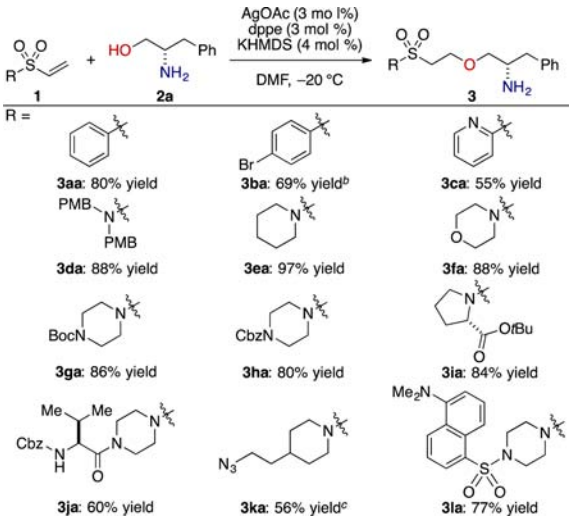


entry	Lewis acid (3 mol %)	base (4 mol %)	O/N[b]	yield of 3aa[c] (%)
1[d]			1/>99	(64)
2	Cu(MeSal)/dppe	^{n}BuLi	>20/1	74
3	CuOAc/dppe	^{n}BuLi	>20/1	72
4	AgOAc/dppe	^{n}BuLi	>20/1	77
5	AgOAc/dppe	LiHMDS	>20/1	79
6	AgOAc/dppe	NaHMDS	>20/1	51
7	AgOAc/dppe	KHMDS	>20/1	80[e]
8[f]	AgHMDS/dppe		20/1	78
9	AgOAc/dppe		1/>99	(13)
10		KHMDS	>20/1	21[g]

[a]Reaction conditions: **1a** (0.8 mmol), **2a** (0.96 mmol), DMF (0.8 mL). [b]Determined by ^{1}H NMR analysis of crude mixture. [c]Determined by ^{1}H NMR analysis using $(CHCl_2)_2$ as an internal standard. Yield of **4aa** is shown in parentheses. [d]Performed at room temperature. [e]Isolated yield. [f]15 mol % of AgHMDS and dppe were used. [g]**1a** was completely consumed to give the complex mixture. "O" refers to *O*-adduct. "N" refers to *N*-adduct.

could be applied (Scheme 1). Aryl vinyl sulfones **3b** and **3c** were also transformed into the corresponding products in good

Scheme 1. Scope of α,β-Sulfonyl Derivatives[a]

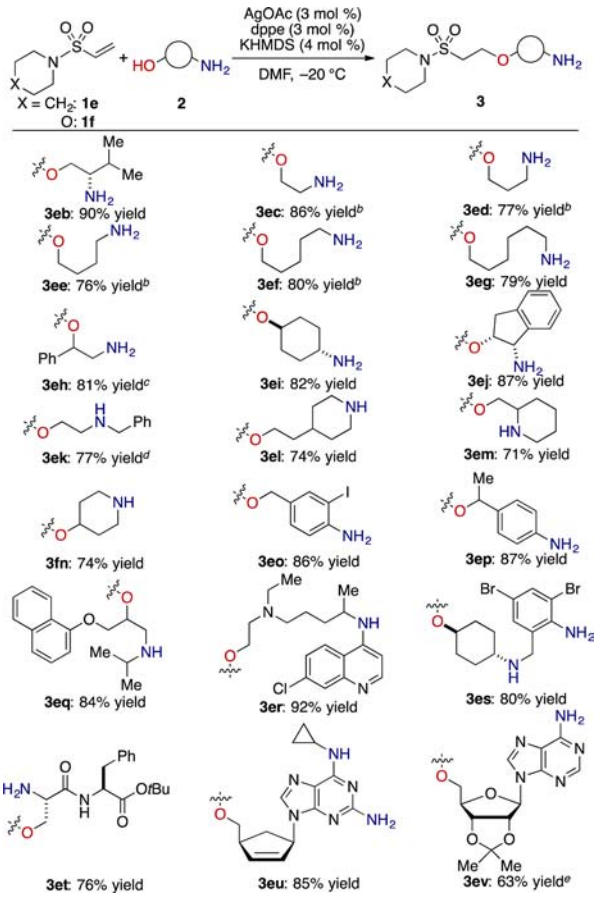


[a]Conditions: **1** (1.0 equiv), **2a** (1.2 equiv). Isolated yield are shown. In all cases, the O/N ratio measured by ^{1}H NMR analysis was >20/1. [b]3 mol % KHMDS was used. [c]3 mol % *n*BuLi was used. [d]THF/DMF mixture was used as solvent.

yield, and these products can be further transformed through late-stage functionalization.[11,12] Less electrophilic sulfonamides **1d–h** were better substrates. Proline ester survived without stereochemical erosion, providing product **3ia** in high yield. Sulfonamide with amino acid derivative **1j** was also applicable. An azide group, whose further elaboration can be performed through click chemistry,[13] was incorporated onto a less reactive hydroxy group without protection of the amino group (**3ka**). A dansyl group for fluorescent labeling was successfully installed onto a hydroxy group in high yield (**3la**).

Next, we evaluated the scope of amino alcohols (Scheme 2). The length of the alkyl chain did not affect the yield or

Scheme 2. Scope of Amino Alcohols[a]



[a]Conditions: **1e** (1.0 equiv), **2** (1.2 equiv). Isolated yields are shown. The O/N ratio measured by ^{1}H NMR analysis was >20/1. [b]Isolated as N-Boc-protected products. [c]O/N = 20/1. [d]O/N = 18/1. [e]O/N/N+N = 10/1/2. "N+N" refers to *N,N*-dialkylated adduct.

chemoselectivity (**3ec–eg**). Secondary hydroxy groups, which were difficult to use in previous studies,[3] were applicable without detrimental effects (**3eh–ej**). Enhanced nucleophilic secondary amino groups were intact, and the desired hydroxy group adducts were isolated in high yield (**3ek–em**). Coupling of **1f** and **2n** was achieved in high yield without any protection.[14] Comparably acidic aryl amines were tolerated (**3eo** and **3ep**). Various pharmaceuticals, such as propranolol (**2q**), hydroxychloroquine (**2r**), and ambroxol (**2s**), were applicable, and hydroxy group adducts **3eq–es** were isolated in high yield. Dipeptide with acidic NH proton was converted into the corresponding product **3et** in high yield without stereochemical erosion. Nucleoside derivatives **2u** and **2v** were also applicable, although the chemoselectivity was slightly decreased when adenosine derivative **2v** was used.

Further utility of the present catalytic chemoselective functional group installation method was demonstrated by the coupling of **1l** and ambroxol (**2s**) (Scheme 3). Facile fluorescent labeling was achieved though hydroxy group selective conjugate addition in the presence of aliphatic and aryl amino groups.

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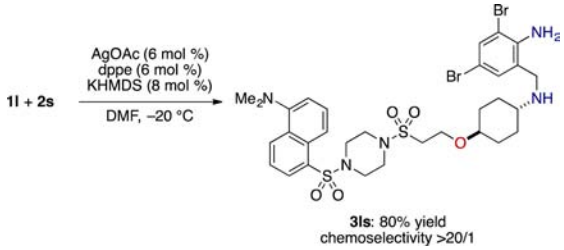
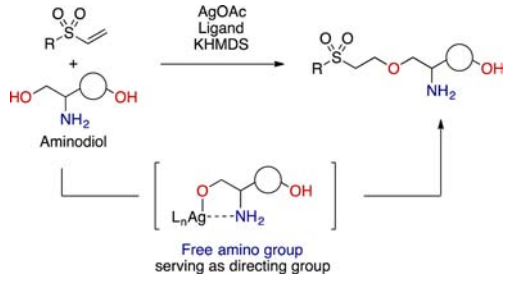
Scheme 3. Catalytic Chemoselective Fluorescent Labeling of Ambroxol (2s)



We next directed our attention toward catalyst-controlled chemo- and regioselective reaction of unprotected amino diol. We envisioned that a hydroxy group at the β-position of the free amino group would be selectively activated through bidentate coordination to Lewis acidic silver salt even in the presence of another distinct hydroxy group, where the free amino group serves as a directing group (Scheme 4). Although

Scheme 4. Working Hypothesis for Catalytic Chemo- and Regioselective Activation of Aminodiol Utilizing the Free Amino Group as the Directing Group

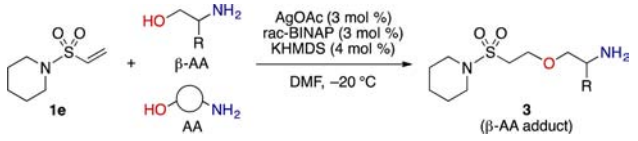


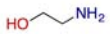
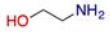
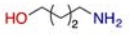
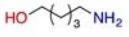
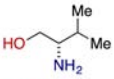
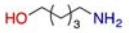
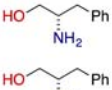
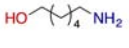
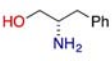
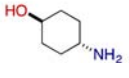
several reactions utilizing a free amino group serving as a directing group have been reported, previous examples are limited to the aniline[15] and benzylamine[16] for the C−H activation reaction. Regioselective acylation of protected amino diol has been reported, whereas catalyst-controlled chemo- and regioselective reaction of unprotected amino diol has never been reported.[17]

We began our study using a 1:1 mixture of 2-aminoethanol (**2c**) and 3-amino-1-propanol (**2d**) (Table 2). Optimized conditions with DPPE as a ligand provided moderate selectivity between **3ec** and **3ed** (entry 1). Evaluation of a variety of ligands revealed that *rac*-BINAP is a competent ligand. Use of *rac*-BINAP instead of DPPE produced better selectivity (entry 2).[18−20] Several combinations of amino alcohols were investigated under the optimized conditions. The selectivity was further increased when amino alcohols had a longer alkyl chain linker (entries 3 and 4). The high selectivity, even when sterically congested valinol was used as the β-amino alcohol, is noteworthy (entry 5). When solid amino alcohols were used, almost perfect selectivity and high yield were achieved (entries 6 and 7).

Finally, 2-aminopentane-1,5-diol (**2w**) was subjected to the optimized conditions (Scheme 5). Although increased catalyst loading was required for efficient promotion of the reaction, the desired β-O-adduct **3ew** was selectively isolated in 55% yield. The results were inferior when DPPE was used as the ligand. In marked contrast, KHMDS catalysis provided **3ew** in 7% yield with reversed low regioselectivity, demonstrating the importance of the Lewis acidic silver complex for high β-amino

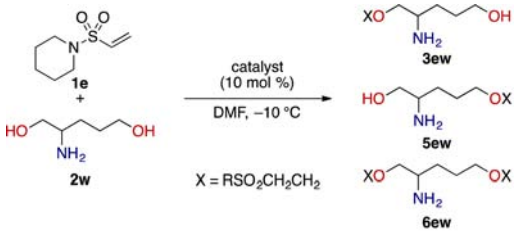
Table 2. Catalytic Chemo- and Regioselective Conjugate Addition[a]



entry	β-AA	AA	yield of β-AA (%)	ratio of β-AA/AA
1[b]			60[c]	70/30
2			48[d]	85/15
3			45	91/9
4			44	95/9
5			62	94/6
6			85	>95/5
7			88	>95/5

[a]Conditions: **1b** (0.8 mmol), **2d** (0.96 mmol), **2e** (0.96 mmol), DMF (1.6 mL). Isolated as *N*-Boc-protected products. Yields of the two steps are given, and isolated yields are shown (>94% purity). In all cases, the O/N ratio was >20/1. "β-AA" refers to β-amino alcohol. "AA" refers to amino alcohol having longer linkers (or side chains). [b]DPPE was used as ligand. [c]Purity of isolated product was 69%. [d]Purity of isolated product was 90%.

Scheme 5. Catalytic Chemo- and Regioselective Conjugate Addition of Amino Diol



catalyst	yield (%) 3ew	yield (%) 5ew	yield (%) 6ew
AgOAc, rac-BINAP, KHMDS	55	<1	8
AgOAc, DPPE, KHMDS	53	9	12
KHMDS	7	14	25

alcohol selectivity. Moreover, almost perfect chemo- and regioselective fluorescent labeling was achieved using **1l**, highlighting the synthetic utility of the free amino group-directed hydroxy group selective reaction (Scheme 6).

In conclusion, we developed protocols for chemoselective functional group installation through a catalytic hydroxy group selective conjugate addition of amino alcohols to various functionalized α,β-unsaturated sulfonyl derivatives. The facile preparation of fluorescent labeling of a less reactive hydroxy group of a pharmaceutical agent highlighted the synthetic utility of the present chemoselective catalysis. In addition, for the first time, a free amino group was effectively applied as a directing group for chemo- and regioselective activation of amino diol. Further application of this catalytic chemo- and regioselective reaction of amino diol is in progress.

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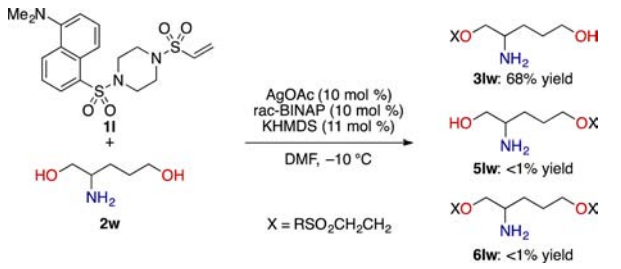
Scheme 6. Catalytic Chemo- and Regioselective Fluorescent Labeling of Amino Diol



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01464.

Experimental details, characterization data, and NMR spectra of all products (PDF)

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Notes

The authors declare no competing financial interest.

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(10) We checked the reaction profile of KHMDS catalysis (Table 1, entry 10). Phenyl vinyl sulfone (**1a**) was completely consumed within 5 min, and the yield of the product **3aa** was constant during the course of the reaction (60 min). We concluded that the addition of soft Lewis acid efficiently suppressed the undesired polymerization.

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(18) We confirmed that the ratio of β-AA/AA was constant (around 70/30) when the reaction was quenched within five minutes using DPPE as ligand (<30% conversion).

(19) We also evaluated the ratio of AgOAc/*rac*-BINAP, and a 1:1 ratio was most effective. Thus, we speculated that the AgOAc/*rac*-BINAP = 1:1 complex would be an actual catalytic species. For silver BINAP complexes, see: Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5360.

(20) At this stage, the ligand effect was not clear. We speculated that a slightly more Lewis acidic silver complex would be generated using *rac*-BINAP, allowing for rapid bidentate coordination of β-amino alcohol. Further studies to elucidate the precise reaction mechanism are in progress.

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