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Novel and Efficient Chromium(II)-Mediated Desulfonylation of α-Sulfonyl Ketone

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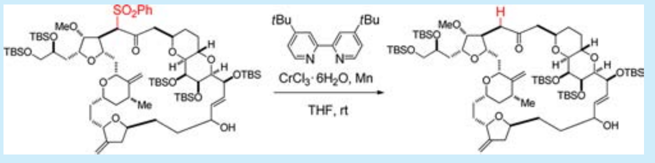
Supporting Information

ABSTRACT: A novel and efficient method for the Cr(II)-mediated desulfonylation of α-sulfonyl ketone by a Cr−ligand−Mn system has been developed during the course of process research on Halaven (eribulin mesylate). This reaction is dramatically accelerated in the presence of an appropriate bipyridyl-type ligand. This system is applicable to reduction of α-sulfur-substituted ketones. In addition, a Cr−Cp_2ZrCl_2−Mn catalytic system is also applicable to desulfonylation of α-sulfonyl ketone.



Halaven (**1**; E7389, eribulin mesylate) is a fully synthetic analogue of the structurally complex marine natural product halichondrin B (HB).[1] Halaven has been approved for use in more than 50 countries for the treatment of certain patients with metastatic breast cancer.[2]

Although the structure of eribulin mesylate is considerably simpler than that of HB (eribulin mesylate has one-third as many stereogenic centers on the carbon backbone as does HB), the total synthesis of eribulin mesylate was a significant challenge.[3] Our efforts to establish a manufacturing process for eribulin mesylate have led to a stable supply of the drug with consistent quality through a validated method.[4−6] However, we are continuously seeking ways to make the manufacturing process more efficient, green, and simple.

The final assembly process for eribulin mesylate is shown in Scheme 1 (**2** → **3** → **4**), where SmI_2-mediated desulfonylation[7] of α-sulfonyl ketone **2** gives ketone **3**, and subsequent intramolecular Nozaki−Hiyama−Kishi (NHK) reaction affords macrocyclized ketone **4**. Macrocyclization proceeds efficiently by adopting a stoichiometric asymmetric version of the NHK reaction in the presence of (*S*)-sulfonamide ligand.[6,8,9] Points of improvement in these transformations over previous methods include (1) use of cryogenic desulfonylation conditions, (2) use of air-sensitive SmI_2, and (3) increased yield in the macrocyclization step. Because **2** has an aldehyde group, cryogenic conditions are essential to suppress the side reaction associated with the aldehyde group. Therefore, if **2** is subjected to NHK reaction first (**2** → **5**), it is expected that other options for desulfonylation can be applied. Regarding the NHK reaction, Namba and Kishi have already reported the application of a catalytic NHK reaction to macrocyclization of **3**.[10] Our research plan was to develop an optimized catalytic NHK reaction for **2** and practical desulfonylation conditions for **5**. During the course of this research, we discovered a novel and efficient desulfonylation reaction promoted by Cr(II) species. We have already investigated a catalytic process for **3** → **4** and found that the reaction proceeds efficiently by using Ni−neocuproine complex **6**, $CrCl_3$, and 4,4′-di-*tert*-butyl-2,2′-bipyridyl **7**. In this reaction, addition of LiCl is not necessary.[10,11] The same conditions were applied to the reaction of **2**, and macrocyclized product **5** was obtained in even better yield (95%). Subsequent desulfonylation of **5** by SmI_2 could be employed without cryogenic conditions (0 °C) to give **4** in excellent yield (92%) with no side reaction.[12] However, we found that a slight amount of **4** was generated during the NHK reaction of **2**. This result implied that there were species other than SmI_2[13] that could remove the sulfone of **5** under the conditions of the NHK reaction and encouraged us to find a novel and efficient desulfonylation system potentially residing in the NHK reaction.

Initially, we investigated which species promoted desulfonylation of **5** (Table 1). We found that only the combination of $CrCl_3$, **7**, and Mn promoted reaction,[14] indicating that Cr(II) was the essential species for desulfonylation. To the best of our knowledge, there are no published reports of Cr(II)-mediated desulfonylation (for a review of other Cr(II)-mediated reactions, see ref 15). Therefore, to develop an alternative method for the Cr(II)-mediated desulfonylation of **5**, we focused on the Cr(III)−Mn system as a source of Cr(II) because it is easy to handle and relatively inexpensive compared with Cr(II) itself.

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Scheme 1. Alternative Route Finding of 2 to 4

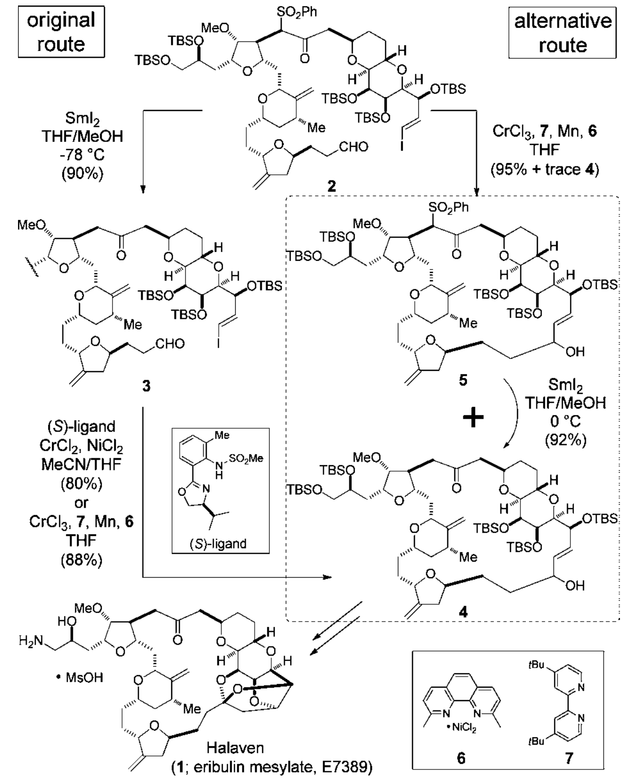
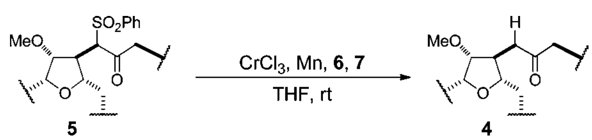


Table 1. Desulfonylation of 5: Investigation of the Essential Sources

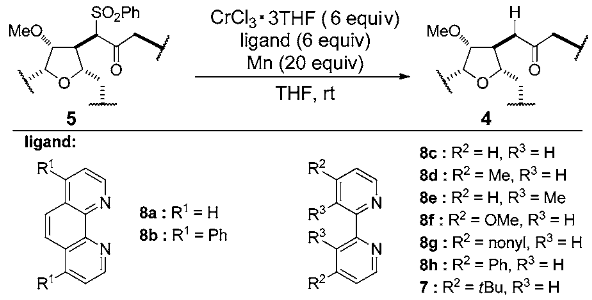


entry	6 (equiv)	$CrCl_3$ and 7 (equiv)	Mn (equiv)	HPLC area ratio 5	4
1	0	6	0	100	0
2	6	0	0	100	0
3	0	0	20	100	0
4	6	6	0	100	0
5	6	0	20	100	0
6	0	6	20	0	100

Ligand screening showed that desulfonylation of 5 was dramatically accelerated in the presence of appropriate bipyridyl-type ligands (Table 2). When ligands having lipophilic substituents at the 4,4′-positions were employed, reactivity was high (entries 3, 8–10). In contrast, reactivity was insufficient when unsubstituted or methoxy-substituted ligands were used (entries 2, 4–7). We determined that 7 was the best ligand owing to its availability and cost.

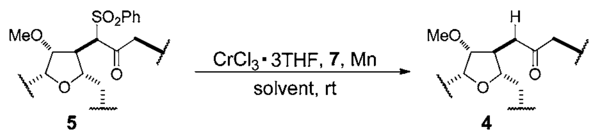
Next, solvent screening was carried out (Table 3). Full conversion was achieved with THF or MeOH (entries 1, 2), whereas 5 remained in the cases of toluene, MeCN, and DMF (entries 3–5). Stoichiometric amounts of Cr(III), 7, and Mn[16] were required to complete the desulfonylation reaction (entry 6). After optimization, 1.5 equiv of Cr(III)–ligand and 4 equiv of Mn were sufficient for complete reaction (entry 7); a 94% yield was obtained at the 540 mg scale with $CrCl_3 \cdot 6H_2O$ as the

Table 2. Desulfonylation of 5: Ligand Screening



entry	ligand	HPLC area ratio 5	4
1	none	100	0
2	8a	100	0
3	8b	0	100
4	8c	100	0
5	8d	100	0
6	8e	63	37
7	8f	79	21
8	8g	10	90
9	8h	10	90
10	7	0	100

Table 3. Desulfonylation of 5: Solvent Screening



entry	solvent	Cr(III)–ligand (equiv)	Mn (equiv)	HPLC area ratio 5	4
1	THF	6	20	0	100
2	MeOH	6	20	0	100
3	toluene	6	20	90	10
4	MeCN	6	20	19	81
5	DMF	6	20	2	98
6	THF	0.75	5	13	87
7	THF	1.5	4	0	100
8[a,b]	THF	1.5	4	0	100

[a] $CrCl_3 \cdot 6H_2O$ was used instead of $CrCl_3 \cdot 3THF$. [b] 94% yield (540 mg scale).

Cr(III) source (entry 8).[17] From these results, we decided that $CrCl_3 \cdot 6H_2O$ was the best Cr(III) source because of its ready availability and low cost.[18]

To demonstrate the potential of this chemistry, we investigated the catalytic desulfonylation of 5. First, to achieve catalytic desulfonylation, a stoichiometric Cr–ligand complex capable of dissociating the strong Cr–O bond of the *in situ*-generated Cr–enolate derived from the carbonyl group at the α-position is needed.[19] In seminal work in 1996, Fürstner and Shi used TMSCl as a dissociating agent of Cr–alkoxides, in a catalytic process for the NHK reaction.[20] In 2004, Namba and Kishi reported that Cp_2ZrCl_2 also works as a dissociating agent of Cr–alkoxides.[21] Based on these findings, exploratory studies aimed at developing a catalytic reduction system showed that desulfonylation of 5 proceeded smoothly at room temperature when $CrCl_3 \cdot 6H_2O$ (20 mol %), 7 (20 mol %), Mn (4 equiv), and Cp_2ZrCl_2 (1.1 equiv) were used (95% yield, Scheme 2). In

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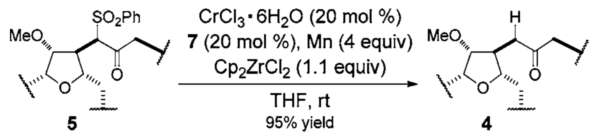
contrast, low conversion was achieved when TMSCl was used instead of Cp_2ZrCl_2 (20% conversion).

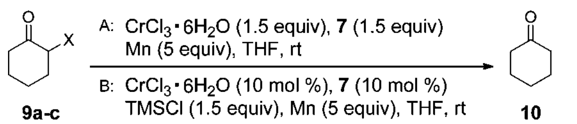
Scheme 2. Cr–Ligand Catalyzed Desulfonylation of 5[a]



[a]The yield was determined by HPLC.

To evaluate the generality of the Cr–ligand–Mn-mediated reduction system, we investigated various α-sulfur-substituted ketones.[22] Reductive cleavage of α-(phenylthio), α-(phenylsulfinyl), and α-(phenylsulfonyl) groups (**9a–c**) proceeded smoothly in the Cr–ligand–Mn system to give corresponding cyclohexanone **10** in good yield (Table 4). In addition, **9c** underwent catalytic desulfonylation in >99% yield.

Table 4. Cr–Ligand–Mn-Mediated Desulfonylation of Various α-Sulfur-Substituted Ketones 9a–c



entry	X	method	yield of **10** (%)[a]
1	SPh (**9a**)	A	85
2	SOPh (**9b**)	A	85
3	SO_2Ph (**9c**)	A	>99
4	SO_2Ph (**9c**)	B	>99

[a]Yield of **10** was determined using crude reaction solution by GC in external standard method.

In summary, during the course of process research on eribulin mesylate (Halaven), a novel and practical Cr–ligand–Mn-mediated reduction system has been developed. This novel approach is applicable to reductive cleavage of sulfur groups in α-sulfur-substituted ketones. We expect that this system will be useful for the total synthesis of natural products and pharmaceuticals with complicated structures such as that of eribulin mesylate.

ASSOCIATED CONTENT

Supporting Information

Experimental details and analytical data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01497.

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Author Contributions

§T.F. and K.T. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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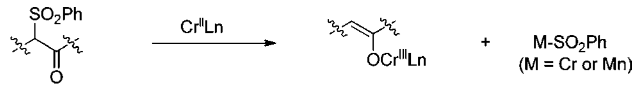
(13) We investigated desulfonylation of **5** with some metals or amalgams such as Zn, Zn-Cu, Mg-MeOH, and lithium naphthalenide. Only lithium naphthalenide gave product **4** in good yield (88%). The others were very low conversion or decomposition. Lithium naphthalenide was needed for cryogenic conditions, and lithium naphthalenide itself had problems handling SmI_2.

(14) Both the combination of $CrCl_2$ and Mn, and **7** and Mn resulted in no reaction.

(15) Review of Cr(II) mediated reactions, see: (a) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991. (b) Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1. (c) Hargaden, G. C.; Guiry, P. J. *Adv. Synth. Catal.* **2007**, *349*, 2407.

(16) Various metals (Zn, Mg, Al, Fe) were investigated. Zn was effective as reducing reagent, but the reactivity was slightly lower compared with Mn. See Supporting Information.
(17) We investigated one step conversion of **2** to **4**. Reaction conditions (not optimized): **6** (0.1 equiv), $CrCl_3$ (2.1 equiv), **7** (2.1 equiv), Mn (10 equiv), Cp_2ZrCl_2 (1.5 equiv), THF, rt, 81% yield.
(18) $CrCl_3$, $CrCl_3 \cdot 6H_2O$, $CrCl_3 \cdot 3THF$, and $CrBr_3 \cdot 6H_2O$ showed same reactivity in this reaction system, and $CrCl_3 \cdot 6H_2O$ was selected in terms of its commercial availability and cost. However, $Cr(OAc)_3$ and $Cr(acac)_3$ showed low reactivity. See Supporting Information.
(19) After the reaction, Cr-enolate (detected in LCMS analysis) and some metal-sulfonium salt were generated.



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