JOC Notes

Highly Diastereoselective Addition of the Lithium Enolate of α-Diazoacetoacetate to *N*-Sulfinyl Imines: Enantioselective Synthesis of 2-Oxo and 3-Oxo Pyrrolidines

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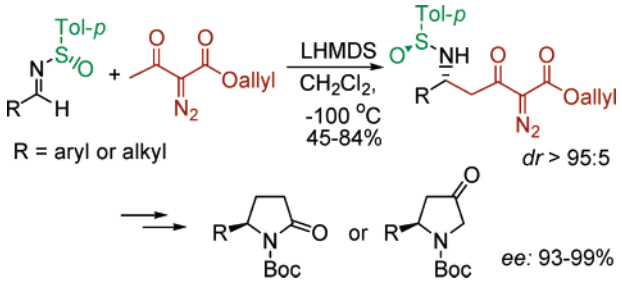

The highly enantioselective synthesis of 2-oxo and 3-oxo pyrrolidines has been achieved by diastereoselective addition of the lithium enolate of α-diazoacetoacetate to chiral *N*-sulfinyl imines, followed by photoinduced Wolff rearrangement or Rh(II)-catalyzed intramolecular N−H insertion.

2-Oxo and 3-oxo pyrrolidines are widespread among natural products and biologically active molecules.[1] Chiral pyrrolidinones are used as excellent building blocks for the synthesis of a plethora of nitrogen-containing natural products, such as pyrrolizidines and indolizidines.[1a−c] Consequently, many methodologies have been developed for their synthesis over the years.[2] The most widely applied ways to synthesize 2-oxo pyrrolidines include ring expansion of β-lactam derivatives,[3] formal [3+2] annulations,[4] and metal carbene intramolecular C−H insertions.[5,6] Compared to 2-oxo pyrrolidines, there are relatively fewer methods for the synthesis of 3-oxo pyrrolidines. The common ways to obtain this type of compounds are intramolecular N−H insertions through decomposition of diazocarbonyl compounds by Lewis acid or protic acid,[7] and radical carbonylation−reductive cyclizations.[8]

Although the above-mentioned reactions provide diverse access to these compounds, there are only limited methods to synthesize them in an enantioselective manner.[3a,c,6e,h,7e,9] Consequently, it is highly desirable to develop efficient methods that allow one to access substituted 2-oxo and 3-oxo pyrrolidines

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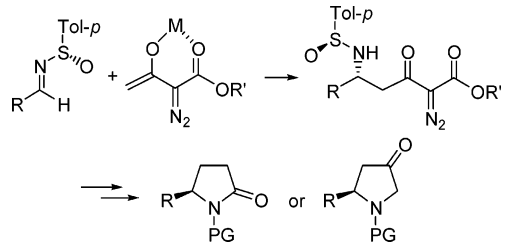
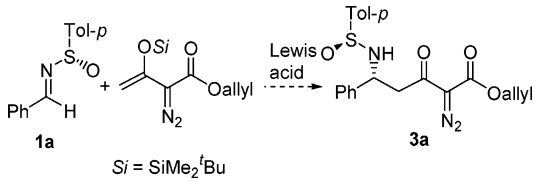
SCHEME 1. Enantioselective Synthesis of 2-Oxo and 3-Oxo Pyrrolidines



SCHEME 2. Enantioselective Synthesis of 2-Oxo and 3-Oxo Pyrrolidines

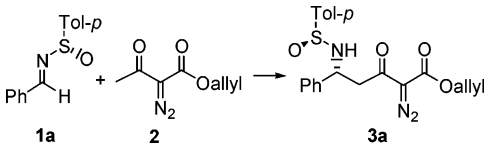


in enantiomerically pure form. We have recently developed a new synthesis of 2-oxo pyrrolidines based on the nucleophilic addition of Ti(IV) enolate to *N*-tosylimines.[10] Here we report the further extension of this method to the enantioselective synthesis of 2-oxo and 3-oxo pyrrolidines (Scheme 1).

In the outset of this work, we attempted catalytic Mukaiyama strategy. Thus, the silyl enol ether of α-diazoacetoacetate was expected to add to *N*-(benzylidene)-*p*-toluene sulfinamide **1a** under catalysis with Lewis acids, such as $Et_2O{\cdot}BF_3$, $TiCl_4$, $Cu(OTf)_2$, $La(OTf)_3$, and TBSOTf.[13] We found that only TBSOTf could provide a low yield of the expected addition product. After some attempts, we reached the conclusion that the reaction with the silyl enol ether of α-diazoacetoacetate could not be optimized (Scheme 2).

We then turned to a straightforward way to generate the enolate by using a strong base (Table 1). When ^{t}BuOK was added to the mixture of α-diazoacetoacetate and *N*-sulfinyl imine, no reaction occurred at all. A similar result was obtained with LDA. Since LDA is obviously strong enough to remove the α proton of a carbonyl compound, we speculated that the byproduct $^i Pr_2NH$ might hamper the following nucleophilic addition. *tert*-Butyllithium was then examined. The expected addition product **3a** was indeed obtained, albeit in low yield. To our delight, the diastereoselectivity of the product was moderately high (entry 3). Since ^{t}BuLi is a very strong base that may cause side reactions, other bases were examined. With potassium bis(trimethylsilyl)amide (KHMDS), both yield and diastereoselectivity were improved (entry 4). However, sodium bis(trimethylsilyl)amide (NaHMDS) resulted in a complex mixture. Eventually, we found lithium bis(trimethylsilyl)amide

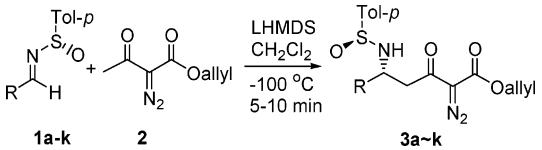
TABLE 1. Optimization of Reaction Conditions with 1a



entry	base	solvent	yield (%)[a]	dr[b]
1	^{t}BuOK	THF	N.R.[c]	
2	LDA	THF	N.R.[c]	
3	^{t}BuLi	THF	25	91:9
4	KHMDS	THF	44	>95:5
5	NaHMDS	THF	*d*	
6	LHMDS	THF	55	>95:5
7	LHMDS	Et_2O	81	91:9
8	LHMDS	$PhCH_3$	59	94:6
9	LHMDS	CH_2Cl_2	78	>95:5

[a] Isolated yield after chromatography. [b] Ratio was determined by ^{1}H NMR (300 MHz) of the crude product. [c] No reaction occurred. [d] The reaction gave a complex mixture.

TABLE 2. The Reaction of 2 with *N*-sulfinylimine 1a−k



entry	imine (**1a**−**k**, R)	yield (%)[a]	dr[b]
1	**1a**, R = Ph	**3a**, 78	>95:5
2	**1b**, R = *p*-FC_6H_4	**3b**, 78	>95:5
3	**1c**, R = *p*-$CH_3OC_6H_4$	**3c**, 66	>95:5
4	**1d**, R = *o*,*p*-$Cl_2C_6H_3$	**3d**, 74	>95:5
5	**1e**, R = piperonyl	**3e**, 70	>95:5
6	**1f**, R= *o*-$CH_3C_6H_4$	**3f**, 84	>95:5
7	**1g**, R = *trans*-$C_6H_5CH{=}CH$	**3g**, 63	>95:5
8	**1h**, R= 2-furyl	**3h**, 69	>95:5
9	**1i**, R = cyclohexyl	**3i**, 45	>95:5
10	**1j**, R = hexyl	**3j**, 53	>95:5
11	**1k**, R = isobutyl	**3k**, 56	>95:5

[a] Isolated yield after chromatography. [b] Ratio was determined by ^{1}H NMR (300 MHz) of the crude product.

(LHMDS) was the most suitable base for this reaction. Further examination of solvent effects led to the following optimized reaction conditions: with CH_2Cl_2 as solvent, LHMDS as base, at −100 °C.

The optimized reaction condition was then applied to a series of *N*-sulfinyl imines (Table 2). All aromatic imines reacted smoothly with allyl diazoacetoacetate and afforded excellent diastereoselectivities and good yields. The substituents on the aromatic ring had little influence on the reaction. When aliphatic imines were subjected to the reaction, the yields somewhat decreased but diastereoselectivities remained high. It was worth noting that in all cases the addition reaction proceeded very fast and could complete within 10 min.

The absolute configuration of the newly generated chiral center was established by X-ray analysis of a single crystal of **3c**. When the chiral center of sulfur has the *S* configuration, the newly formed chiral center has the *R* configuration (Figure 1).

This stereochemical outcome is consistent with the previous reports of the addition of enolates derived from ester or ketones

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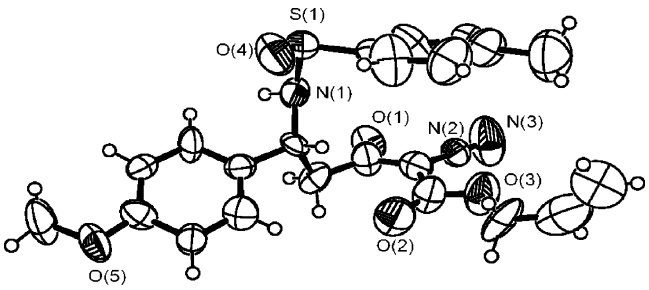
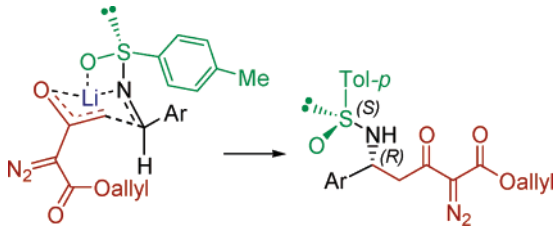


FIGURE 1. X-ray structure of **3c**.

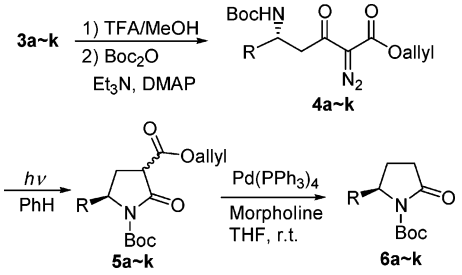
SCHEME 3. Transition State of the Diastereoselective Addition Reaction



to *N*-sulfinyl imines.[12,14] On the basis of the stereochemical information, we conclude that the sense of induction can be similarly predicted by invoking a six-membered Zimmerman−Traxler-type transition state as previously suggested for the similar addition of acetate enolates to *N*-sulfinyl imines (Scheme 3). In this transition state, the chelation of the Li^+ with the sulfinyl oxygen plays a vital role in controlling the attack of the enolate to the *Re* face of the imine.[14]

With the addition products in hand, we proceeded to convert these chiral diazo compounds to 2-oxo and 3-oxo pyrrolidines by the reaction sequence that we have reported previously.[10b] First, the diazo compound **3a** (R = Ph) was photolyzed with a high-pressure Hg lamp (λ > 300 nm) in a Pyrex tube. The Wolff rearrangement was expected to occur to form the ketene intermediate,[15] followed by intramolecular nucleophilic attack by the amino group to afford 2-oxo pyrrolidines.[16] However, the expected 2-oxo pyrrolidines were not obtained, instead, the photolysis resulted in a dark complex mixture. Considering our previous study with *N*-sulfonyl diazo compounds, which gave the corresponding 2-oxo pyrrolidines in good yield,[10b] we concluded that the *N*-sulfinyl group was not compatible with the photochemical condition. So the *N*-sulfinyl group was replaced by *tert*-butyloxycarbonyl (Boc), and the *N*-Boc diazo compound **4a** was subjected to the photolysis. To our delight, the corresponding 2-oxo-3-allyloxycarbonyl pyrrolidine **5a** was obtained in excellent yield, but the diastereoselectivity of this reaction was poor due to the easy epimerization at C3. Consequently, the allyloxycarbonyl was removed by Pd(0)-catalyzed reaction[17] and 5-substituted 2-oxo pyrrolidine **6a** was obtained with 98% ee. This reaction sequence was then applied to other diazo compounds **3b**−**k**, and the corresponding 5-substituted 2-oxo pyrrolidines **6b**−**k** were obtained in excellent overall yields with high enantiomeric selectivities (Table 3).

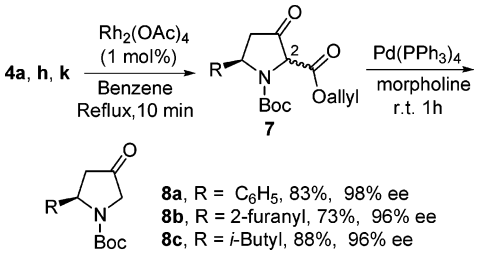
TABLE 3. Reaction of 2a with Various Aromatic Compounds



entry	imine (**3a**−**k**, R)	**4**, yield (%)[a]	**5**, yield (%)	**6**, yield (%)	ee (%)[b]
1	**3a**, R = Ph	98	77	87	98
2	**3b**, R = *p*-FC_6H_4	96	66	87	99
3	**3c**, R = *p*-$CH_3OC_6H_4$	98	60	93	96
4	**3d**, R = *o*,*p*-$Cl_2C_6H_3$	97	60	87	98
5	**3e**, R = piperonyl	96	51	85	96
6	**3f**, R= *o*-MeC_6H_4	98	75	88	94
7	**3g**, R = *trans*-C_6H_5CH=CH	99	84[c]	86	95[d]
8	**3h**, R= 2-furyl	98	53	74	96
9	**3i**, R = cyclohexyl	92	94	99	95
10	**3j**, R = hexyl	92	92	96	94[e]
11	**3k**, R = isobutyl	91	89	93	94[e]

[a] Isolated yield after chromatography. [b] Ee was determined by HPLC with chiral column. [c] Under photochemical conditions, partial isomerization of the double bond occurred. [d] **6g** was derivatized and the derivative was measured as the 96% ee value. See the Supporting Information. [e] The ee value was determined after removing the Boc group. See the Supporting Information.

SCHEME 4. Conversion of 4a,h,k to 3-Oxa Pyrrolidines 8a−c



Next, we conceived that intramolecular N−H insertion of metal carbene generated from diazo compound **3** or **4** would afford 3-oxo pyrrolidine derivatives.[7] Davis and co-workers have previously reported the $Rh_2(OAc)_4$-catalyzed intramolecular N−H insertion of δ-amino α-diazo β-ketoesters to give 3-oxo pyrrolidines.[7e] We found that reaction of **3a** with $Rh_2(OAc)_4$ catalysis resulted in a complex mixture. When *N*-Boc protected δ-amino diazo compound **4a** was subjected to the same $Rh_2(OAc)_4$ catalysis, the expected intramolecular N−H product was obtained as a mixture of diastereoisomers and tautomers. The mixture was further catalyzed with $Pd(PPh_3)_4$ to remove the alloxycarbonyl group. 5-Phenyl-substituted 3-oxo pyrrolidine **8a** was thus obtained with 98% ee and in 83% overall yield from **4a**. This transformation was also applied to **4h** and **4k**, and similar results were obtained (Scheme 4). Therefore, starting from chiral *N*-Boc protected δ-amino α-diazo β-ketoesters, both 2-oxo and 3-oxo 5-substituted pyrrolidines could be prepared efficiently.

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In summary, the highly diastereoselective addition of the lithium enolate of α-diazoacetoacetate to *N*-sulfinylimines has been achieved to afford *δ*-*N*-sulfinylamino α-diazo *β*-ketoesters. The chiral *δ*-*N*-sulfinylamino α-diazo *β*-ketoesters can be easily converted into 5-substituted 2-oxo and 3-oxo pyrrolidines. This transformation represents a new route to 5-substituted 2-oxo and 3-oxo pyrrolidines with high enantiomeric purity.

Experimental Section

Caution: Diazo compounds are generally toxic and potentially explosive. They should be handled with care in a well-ventilated fume hood.

General Procedure for the Diastereoselective Addition of Allyl α-Diazoacetoacetate 2 with *N*-Sulfinylimine 1. To a solution of **1** (1 mmol) in dichloromethane (12 mL) was added LHMDS (2 mmol of 1.0 M in hexane) at −100 °C and then **2** (1.5 mmol) in dichloromethane (8 mL) was dropped into the solution. After being stirred for approximate 5−10 min, the reaction was quenched with saturated aqueous NH_4Cl at −100 °C and then warmed quickly to room temperature. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The organic layers were then combined and dried over Na_2SO_4. The crude product was purified by flash silica gel column chromatography to yield the addition products **3a**−**k**.

General Procedure for the Replacement of the Sulfinyl Group in 3 by the Boc Group. The addition product **3a**−**k** (0.5 mmol) was treated by TFA (5.0 equiv) in MeOH (5 mL) and the sulfinyl group in **3** was removed in 1 h to give the corresponding amine salt. The solution was concentrated, and then was dissolved in THF. The solution was treated at 0 °C with Boc_2O (1.2 equiv)/Et_3N (6 equiv) and a catalytic amount of DMAP. After being stirred for about 2 h, the solution was concentrated and purified by silica gel. The *N*-Boc protected product **4a**−**k** was obtained nearly quantitatively for the two steps.

General Procedure for the Irradiation of the Diazo Compound 4a−**k.** A solution of **4a**−**k** (0.5 mmol) in benzene (25 mL) in a Pyrex tube was irradiated with a 300-W Hg lamp with a water-cooled tube inserted in the solvent. The reaction temperature was kept at about 35 °C. The reaction was complete in about 30 min. The solution was concentrated under reduced pressure to give the crude product, which was purified by flash silica gel column chromatography to yield the diastereomeric mixture of the corresponding 3-allyloxycarbonyl-2-oxo pyrrolidines **5a**−**k**. The diastereomeric mixture could not be separated by column chromatography because of the isomerization of the products on silica gel.

General Procedure for the Removal of Allyloxycarbonyl Group of 5 with $Pd(PPh_3)_4$. 5a−**k** (0.2 mmol) was dissolved in THF (5 mL) and $Pd(PPh_3)_4$ (5 mol %) and morpholine (1.5 equiv) were added at room temperature. When the reaction was complete as monitored by TLC, the solution was concentrated under reduced pressure and purified by flash column chromatography with silica gel to afford the pyrrolidine derivative **6a**−**k**.

General Procedure for the $Rh_2(OAc)_4$-Catalyzed Reaction of Diazo Compound 4a,h,k, Followed by $Pd(PPh_3)_4$-Catalyzed Removal of the Allyloxycarbonyl Group. A solution of **4a**,**h**,**k** (0.5 mmol) and $Rh_2(OAc)_4$ (0.005 mmol) in benzene (15 mL) was heated to reflux. The reflux was continued for about 10 min and then the solution was cooled to room temperature. $Pd(PPh_3)_4$ (5 mol %) and morpholine (1.5 equiv) were added and the mixture was stirred for about 1 h under argon. When the reaction was complete as monitored by TLC, the solution was concentrated under reduced pressure and purified by flash column chromatography with silica gel to afford the 3-oxo pyrrolidines **8a**,**b**,**c**.

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Supporting Information Available: Characterization data, CIF for **3c**, and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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