Asymmetric Synthesis

A Highly Stereoselective Addition of the Anion Derived from α-Diazoacetamide to Aromatic *N*-Tosylimines**

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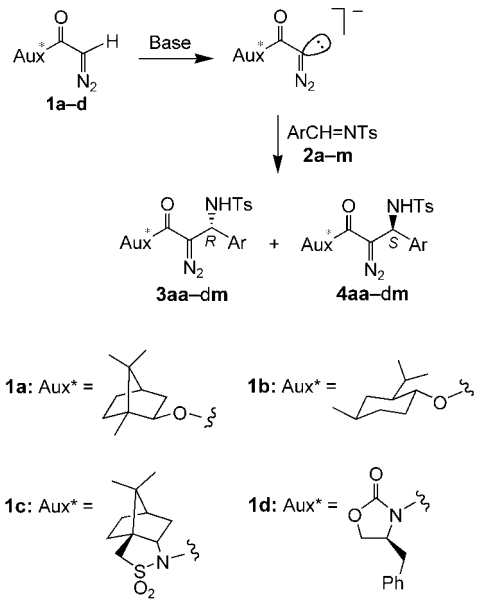
α-Diazocarbonyl compounds have found wide application in organic synthesis as a result of their diverse reactivities.[1] The previous research activities in this area have mostly concentrated on the transition metal complex catalyzed diazo decompositions, which generate metal–carbene intermediates. In addition to serving as metal–carbene precursors, however, the relatively stable α-diazocarbonyl compounds can tolerate a variety of transformations with retention of the diazo functionality, thus allowing the chemical modification of α-diazo compounds.[1c,2] One such transformation is the base-promoted, aldol-type nucleophilic addition of acyldiazomethane to aldehydes or ketones to afford diazoketols.[3] A similar addition to *N*-tosylimines gives α-diazocarbonyl compounds bearing a β-(*N*-tosyl)amino substituent, which demonstrate a novel reactivity in various transition-metal-catalyzed reactions.[4] To further explore the chemistry of this type of nucleophilic addition, we decided to study the stereocontrol of the reaction. Herein, we report a highly diastereoselective base-promoted condensation of an α-diazocarbonyl compound and *N*-tosylimines in the presence of Evans' chiral oxazolidinone auxiliary.[5] The condensation products can be further converted into *syn*- and *anti*-α-hydroxy-β-amino esters.[6]

Our investigation began with the reaction of *N*-tosylbenzaldimine (**2a**) with the α-diazocarbonyl compounds **1a–d**[7] that contain chiral auxiliaries (Scheme 1, Table 1). The



Scheme 1. Base-promoted reaction of chiral diazo compounds **1a–d** with *N*-tosylimines **2a–m**.

Table 1: Base-promoted reaction of **1a–d** with *N*-tosylbenzaldimine **2a**.

Entry	Diazo compound	Base	*T* [°C]	Additive[a]	d.r.[b]	Yield [%][c]
1	**1a**	LDA	−78–RT	–[d]	51:49	50
2	**1b**	LDA	−78–RT	–	55:45	52
3	**1c**	LDA	−78	–	17:83	46
4	**1d**	LDA	−78	–	88:12	87
5	**1d**	LDA	−23	–	84:16	14
6	**1d**	LDA	−98	–	90:10	90
7	**1d**	NaHMDS	−98	–	76:24	95
8	**1d**	DBU	−98–RT	–	–	–[e]
9	**1d**	Et_2Zn	−98–RT	–	–	–
10	**1d**	LDA	−98	LiCl	88:12	81
11	**1d**	LDA	−98	$MgBr_2$	75:25	97
12	**1d**	LDA	−98	HMPA	95:5	84

[a] Five equivalents of additive were employed. [b] Diastereomeric ratio was determined from the ^{1}H NMR (400 MHz) spectrum of the crude product, or by HPLC analysis. [c] Yield of the inseparable diastereomeric mixture after silica gel column chromatography. [d] No additive was used. [e] No reaction.

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reaction with diazo esters **1a** and **1b** gave the addition products in moderate yields, although with essentially no stereoselectivity (Table 1, entries 1 and 2). The reaction with diazoamides **1c** and **1d**, on the other hand, gave good diastereomeric ratios of 17:83 and 88:12, respectively (Table 1, entries 3 and 4). Further improvement of the reaction was then focused on *N*-(diazoacetyl)oxazolidinone (**1d**). The reaction temperature was found to have an influence—reaction at higher temperature (−23 °C) resulted in a lower yield (Table 1, entry 5), presumably because of the instability of the diazo compounds. A slightly higher selectivity can be achieved at −98 °C without affecting the yield or the reaction time (Table 1, entry 6). Changing the base from lithium diisopropylamide (LDA) to sodium hexamethyldisilazide (NaHMDS) gave an improved yield, but with lower stereoselectivity (Table 1, entry 7). Both 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and Et_2Zn, which are known to promote condensation of acyldiazomethane with aldehydes and imines,[3i,8] failed to promote the reaction of **1d** with **2a** (Table 1, entries 8 and 9). Commonly used additives, such as LiCl or $MgBr_2$, were found to have no effect on the stereoselectivity. However, we quite unexpectedly found that HMPA, which binds strongly to lithium ions,[9] significantly improved the stereoselectivity (Table 1, entry 12).[10] It is likely that HMPA disrupts the ion pairing by coordinating to lithium, thus allowing the α-diazocarbonyl anion to react more efficiently at low temperature.

Table 2 illustrates the scope and limitation of the optimized reaction conditions for the reaction of **1d** with a series of aryl *N*-tosylimines **2a–m**. The reaction of most imine substrates gave high diastereoselectivities and yields, although the stereoselectivities were lower with *N*-tosylimines bearing *ortho* substituents (Table 2, entries 8–10). In the case of *N*-tosyl-2,6-dichlorobenzaldimine, the reaction was essentially nonselective (Table 2, entry 10).

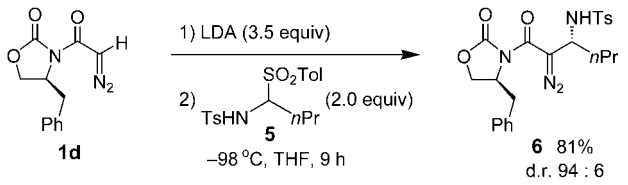
Table 2: Base-promoted reaction of **1d** with aryl *N*-tosylimines **2a–m**.[a]

Entry	Ar group of imine **2**	Product	d.r.[b]	Yield [%][c]
1	C_6H_5	**3da**	95:5	84
2	*p*-PhC_6H_4	**3db**	>95:5	90
3	*p*-ClC_6H_4	**3dc**	>95:5	82
4	*p*-FC_6H_4	**3dd**	>95:5	84
5	*p*-$MeOC_6H_4$	**3de**	93:7	79
6	*m*-CNC_6H_4	**3df**	>95:5	83
7	*m*-BrC_6H_4	**3dg**	95:5	73
8	*o*-MeC_6H_4	**3dh**	76:24	76
9	2,4-$Cl_2C_6H_3$	**3di**	90:10	94
10	2,6-$Cl_2C_6H_3$	**3dj**	56:44	85
11	$C_6H_5CH{=}CH-$	**3dk**	91:9	76
12	2-(5-bromo)thienyl	**3dl**	94:6	73
13	2-furyl	**3dm**	>95:5	78

[a] Reaction was carried out with LDA (1.2 equiv), **1d** (1.0 equiv), and HMPA (5.0 equiv), followed by slow addition of a solution of **2** (1.5 equiv) in THF at −98 °C. [b] The diastereomeric ratio was determined from the ^{1}H NMR (400 MHz) spectrum of the crude product. [c] Yield after purification by silica gel column chromatography.

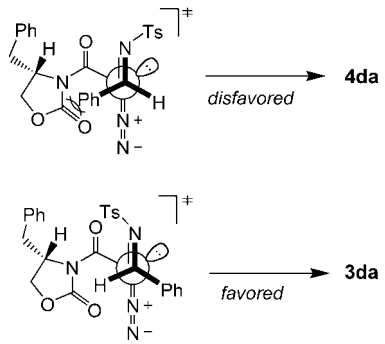
Although most of the addition products were isolated as amorphous solids, one of them (**3dm**) yielded crystals that allowed us to determine the stereochemistry of the newly created chiral center. A single-crystal X-ray diffraction study of this product indicated that the new chiral center has an *R* configuration.[11]

Preliminary experiments also indicated that the LDA-promoted diastereoselective reaction of **1d** with imines can be further extended to aliphatic *N*-tosylimines. Thus, *N*-tosyl-*n*-butylimine, which was generated in situ from the sulfonamide sulfone **5**,[12] was treated with **1d** under similar reaction conditions, but without HMPA additive, to give the addition product **6** in 81% yield and a diastereomeric ratio of 94:6 (Scheme 2).



Scheme 2. LDA-promoted reaction of **1d** with sulfonamide sulfone **5**.

The stereochemical outcome of the reaction can be rationalized by the transition states depicted in Scheme 3.



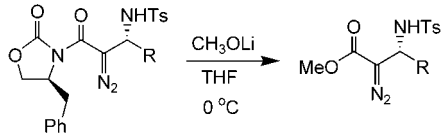
Scheme 3. Plausible stereochemical pathway for the addition of deprotonated **1d** to **2a**.

Initial deprotonation of **1d** generates the diazocarbonyl anion or enolate.[13] Since the HMPA additive coordinates strongly to the lithium ion, the diazocarbonyl anion becomes less associated.[14] Moreover, the *N*-tosylamino group coordinates only weakly to lithium because of the strongly electron-withdrawing tosyl group. Consequently, the nucleophilic addition proceeds through a nonchelated open transition state in which the *N*-tosylimine approaches from the less sterically hindered side of the anion with an orientation that avoids steric repulsion between the aryl group and the oxazolidinone auxiliary. The anions derived from diazo amides **1c** and **1d** are conformationally more rigid than the corresponding anions derived from diazo esters **1a** and **1b** because of the rotational restriction of the amide C–N bond. The rigid structure of the anion might be responsible for the high diastereoselectivities observed for the reactions of **1c** or **1d** in the absence of chelation,[15] while the reaction with

diazo esters **1a** or **1b** is nonselective because of the flexibility of the anion conformation. This stereochemical process is in contrast with the addition of the enolates of acyl oxazolidinones to C=O or C=N bonds,[5,16] where complexation is usually responsible for the high stereoselectivities. Interestingly, the reaction of aromatic aldehydes with **1d** under similar conditions gave rather poor diastereoselectivities and low yields.

The utility of the addition products **3** was demonstrated by the concise synthesis of *syn*- and *anti*-α-hydroxy-β-amino acid derivatives. Thus, the chiral oxazolidinone auxiliary was removed by addition of lithium methoxide in THF to give the chiral methyl α-diazoesters **7a–g,k–m**, and **8** (Table 3).[17]

Table 3: Removal of the chiral oxazolidinone auxiliary.

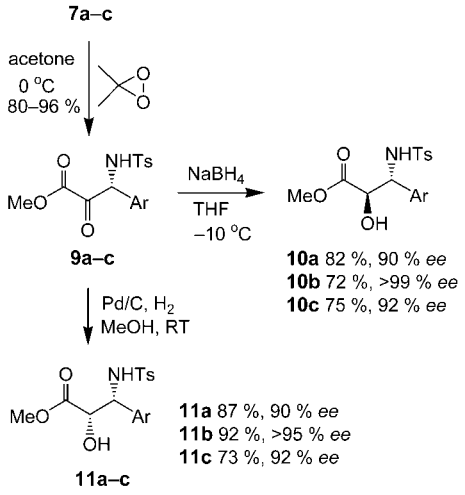


3da–dg,dk–dm, 6 **7a–g,k–m, 8**

Entry	R	Product	*ee* [%][a]	Yield [%][b]
1	C_6H_5	**7a**	90	65
2	*p*-PhC_6H_4	**7b**	>99	67
3	*p*-ClC_6H_4	**7c**	92	58
4	*p*-FC_6H_4	**7d**	95	83
5	*p*-$MeOC_6H_4$	**7e**	85	66
7	*m*-CNC_6H_4	**7f**	91	78
8	*m*-BrC_6H_4	**7g**	90	69
9	$C_6H_5CH{=}CH-$	**7k**	83	73
10	2-(5-bromo)thienyl	**7l**	88	77
11	2-furyl	**7m**	>99	56
12	*n*Pr	**8**	87	60

[a] *ee* value determined by chiral HPLC (see Supporting Information for details). [b] Total yield.

The diazo groups of **7a–c** were subsequently oxidized with dimethyldioxirane (DMD) to give α-ketoesters **9a–c**, respectively (Scheme 4). Reduction of the oxo group with $NaBH_4$ in THF at −10 °C was highly efficient and stereoselective to afford the *anti*-α-hydroxy-β-amino esters **10a–c**.[18,19] Pd/C-catalyzed hydrogenation of the α-ketoesters **9a–c**, on the other hand, gave the *syn*-α-hydroxy-β-amino esters **11a–c**,[20] respectively, also with high yields and selectivities (Scheme 4).[18,19b]



Scheme 4. Synthesis of both *anti*- and *syn*-α-hydroxy-β-amino acid derivatives from chiral methyl α-diazoesters **7a–c**.

In summary, this study is the first example of the highly diastereoselective nucleophilic addition of the anion derived from α-diazocarbonyl compounds to a C=N bond. This reaction can be successfully applied to the synthesis of both *anti*- and *syn*-α-hydroxy-β-amino acid derivatives. Since the diazo group has diverse reactivity, it should be possible to apply the addition products obtained by this reaction to other organic syntheses.

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[18] Only one diastereoisomer could be identified in the ^1H NMR (400 MHz) spectrum of the crude product of each reaction.

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