Tetrahedron Letters 50 (2009) 333–336

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Diastereoselective electrophilic α-amination of camphor N^1-acyl N^2-phenylpyrazolidinones: the metal enolate-dependent synthesis of two possible hydrazide diastereomers

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ARTICLE INFO

Article history:
Received 10 September 2008
Revised 30 October 2008
Accepted 4 November 2008
Available online 7 November 2008

Keywords:
Amination
Reversal of stereoselectivity
Chiral auxiliary

ABSTRACT

Complementary approaches under enolate amination reactions for the synthesis of both α-hydrazidoacyl diastereomers have been achieved. Both isomers are obtained with high to excellent chemical yields and high stereoselectivities (up to >95:5 dr) when aryl-substituted camphor N^1-acyl N^2-phenylpyrazolidinone was treated with potassium hexamethyldisilylamide (KHMDS) and lithium hexamethyldisilylamide (LHMDS), respectively, followed by the addition of di-*tert*-butyl azodicarboxylate. The nondestructive removal of the chiral auxiliary, which can be carried out under mild condition, afforded the hydrazido alcohol with high enantiomeric ratio. The facial stereoselectivity and stereochemical course of the reactions are discussed.

The electrophilic α-amination of carbonyl compounds constitutes one of the fundamental challenges in modern organic synthesis.[1] Several asymmetric variants have been developed in recent years for the construction of the nitrogenous molecules by using azodicarboxylates as the nitrogen source. The resulting hydrazine derivatives serve as versatile precursors for the preparation of α-amino acids, α-hydrazino acids, and other important synthetic intermediates.[2] The metal-based catalytic enantioselective α-amination of *N*-acyloxazolidinones,[3] α-keto esters,[4] and β-keto esters[5] provides an easy entry to optically active α-amino acids and α-amino-β-hydroxy esters with high to excellent enantioselectivities. More recently, the organocatalytic electrophilic α-amination of unmodified aldehydes, α-cyanoacetate, and β-keto esters has also been reported.[6] On the other hand, only limited examples of diastereoselective electrophilic amination of metal enolates have been documented.[7] The metal enolate-based methodology for the carbon–nitrogen bond formation remained unexplored. Further, from a practical synthetic point of view, the preparation of both stereoisomers from the same chiral source has many synthetic advantages and has received considerable attention in recent years.[8] The stereochemical outcomes can be influenced by several factors such as solvent, the structure of metal-substrate complex, and reagent components employed. We have recently developed a novel camphor-derived auxiliary, camphor *N*-phenyl pyrazolidinone, that has proved to be effective in asymmetric synthesis.[8f,j] We wish to report herein that electrophilic amination of chiral

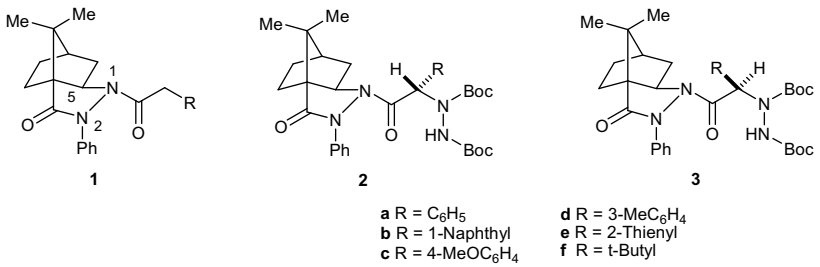

Figure 1.

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doi:10.1016/j.tetlet.2008.11.003

N^1-acyl N^2-phenylpyrazolidinones to give α-aminated derivatives with excellent chemical yield and high diastereoselectivity in the presence of di-*tert*-butyl azodicarboxylate. In addition, the stereochemical course of the α-amination is metal enolate dependent. The facial stereoselectivity and the stereochemical course of the reactions are discussed.

The starting camphor N^1-acyl N^2-phenylpyrazolidinones **1a–f** can be readily prepared from camphor *N*-phenylpyrazolidinone following standard acylation conditions (Fig. 1). The phenylacetyl-substituted pyrazolidinone **1a** was chosen as a probe substrate, and di-*tert*-butyl azodicarboxylate was used as the electrophilic nitrogen source. The desired hydrazides were obtained with low to moderate chemical yields by treatment of **1a**, when LDA, *n*-BuLi, and KO^{t}Bu were used followed by the addition of di-*tert*-butyl azodicarboxylate at −78 °C (data not shown). A reasonable chemical yield (53%) was achieved, when **1a** was treated with KHMDS in CH_2Cl_2 at −78 °C followed by the addition of an electrophile (Table 1, entry 1). No reaction occurred when the reaction was carried out in Et_2O (entry 2). The chemical yield was improved to 91%, when the same reaction was carried out in THF (entry 3). We were not able to interpret the ^{1}H NMR spectrum of the crude products for the determination of stereoselectivity. This is due to the presence of isomer and the tautomeric forms caused by the restricted rotation about the Boc groups in the hydrazide, which has been documented in the literature.[9] The spectrum of a purified hydrazide **2a** is interpretable, although with the presence of tautomers. A careful analysis of ^{1}H NMR spectrum of hydrazide **2a** indicated the characteristic C-5 methine proton (this nomenclature system) that appears at 3.49 ppm, while the carbonyl α-methine proton located at 6.01 ppm. However, two NH proton signals appear at 6.76 and 6.49 ppm, respectively, in a ratio of 1.9:1.0. High performance liquid chromatography (HPLC) studies indicated only one diastereomer in the purified product. A 2D NMR experiment (HMQC) was carried out, and the results indicate that both signals appearing at 6.76 and 6.49 ppm come from the same NH proton. In addition, variable-temperature studies of ^{1}H NMR spectra demonstrated the existence of structural conformers in hydrazide **2a**. An equilibrium mixture of at least two structural conformers of **2a** in $CDCl_3$ was proposed.[10] The newly generated stereogenic carbon center in the major diastereomer **2a** was assigned as an *S* configuration by single crystallographic X-ray analysis.

In addition to the steric hindrance, the tautomeric equilibration of **2a** in solution may also associate with the hydrogen bonds and the preferential disposition of the carbonyl dipoles. A close look of the X-ray crystallographic ORTEP structure of **2a** shows that the NH forms hydrogen bonds with the nearby carbonyl groups (Fig. 2).

To our surprise, the newly generated stereogenic center of the aminated adduct was reversed, when LHMDS was used. Treatment of **1a** with LHMDS at −78 °C gave **3a** as the major diastereomer with 90% de (entry 4). The distinct characteristics of ^{1}H NMR spectrum in **3a** are worth noting. In addition to the two signals of the hydrazide NH proton at 6.68 and 6.49 ppm, the C-5 methine proton also appeared as a set of two signals at 4.41 and 4.31 ppm, respectively, in the same ratio of 1.8:1.0, similar to that of NH signals. The significant chemical shift difference of C-5 proton signal in ^{1}H NMR spectrum between hydrazides **2a** (3.49 ppm) and **3a** (4.41 and 4.31 ppm) can be attributed to the diamagnetic anisotropy effect of the phenyl substituent. *This represents, to the best of our knowledge, the first example of a complementary electrophilic α-amination reaction for the synthesis of both diastereomeric hydrazides by simply changing the base.*[11] Having developed reaction conditions that afford complementary diastereomers in the amination reactions, we sought to test the scope and feasibility of the auxiliary architecture.

Table 1
Diastereoselective amination of camphor N^1-acyl N^2-phenylpyrazolidinones **1a–e**[a]

Entry	R =	Solvent	Base	Yield (%)[b]	Dr (**2**:**3**)[c]
1	(**1a**) C_6H_5	CH_2Cl_2	KHMDS	53	87:13
2	(**1a**) C_6H_5	Et_2O	KHMDS	0	—
3	(**1a**) C_6H_5	THF	KHMDS	91	93[d]:07
4	(**1a**) C_6H_5	THF	LHMDS	94	05:95
5	(**1a**) C_6H_5	THF	Mixed bases[e]	92	77:23
6	(**1a**) C_6H_5	THF	Mixed bases[f]	90	44:56
7	(**1b**) 1-Naphthyl	THF	KHMDS	90	93:07
8	(**1b**) 1-Naphthyl	THF	LHMDS	91	05:95
9	(**1c**) 4-MeOC_6H_4	THF	KHMDS	90	95:05
10	(**1c**) 4-MeOC_6H_4	THF	LHMDS	88	08:92
11	(**1d**) 3-MeC_6H_4	THF	KHMDS	75	95:05
12	(**1d**) 3-MeC_6H_4	THF	LHMDS	81	05:95
13	(**1e**) 2-Thienyl	THF	KHMDS	90	90:10
14	(**1e**) 2-Thienyl	THF	LHMDS	63	08:92

[a] Unless otherwise specified, all reactions were carried out in the solvent indicated at −78 °C using **1** (0.81 mmol), base (0.93 mmol), and di-*tert*-butyl azodicarboxylate (0.85 mmol).
[b] Total isolated yield (**2**+**3**).
[c] Ratios of diastereomers were determined by ^{1}H NMR analysis of relevant peaks and by HPLC analyses of crude products (Agilent Technologies, ZORBAX SIL, 4.6 × 250 mm, hexanes/IPA = 96.7/3.3, flow rate = 0.5 mL/min).
[d] The absolute stereochemistry of the newly generated stereogenic center in **2a** was established by single crystallographic X-ray analysis. The absolute stereochemistry of **2b–e** and **3b–e** is assigned by ^{1}H NMR spectra analyses (see text).
[e] KHMDS (0.6 equiv) was added followed by the addition of LHMDS (0.6 equiv).
[f] LHMDS (0.6 equiv) was added followed by the addition of KHMDS (0.6 equiv).

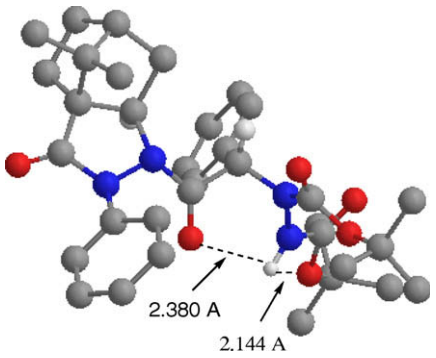
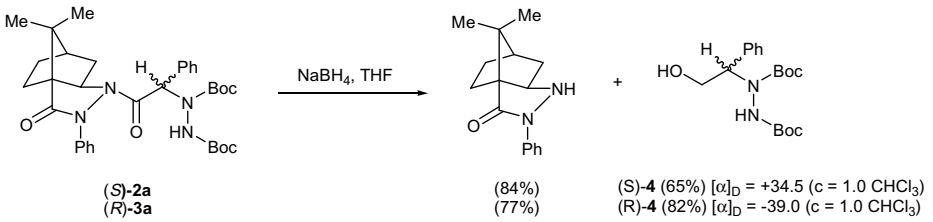


Figure 2. A Chem3D structural drawing of **2a** regenerated from the X-ray crystal coordinates. All hydrogens (except for C2 proton) are omitted for the sake of clarity.



Scheme 1. Recovery of chiral auxiliary from hydrazides **2a** and **3a**.

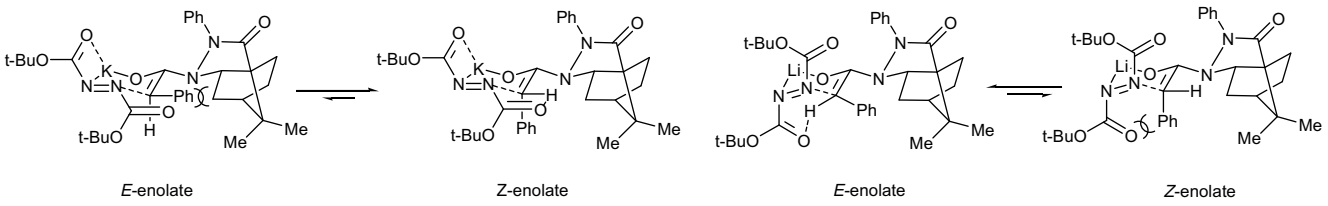
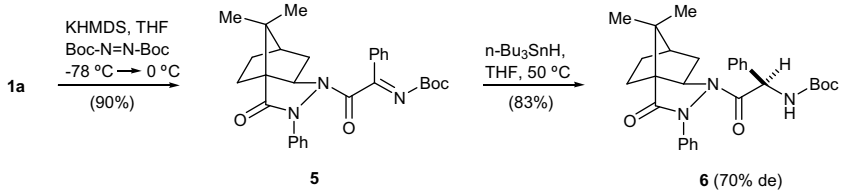


Figure 3. Proposed transition state of the electrophilic amination of **1a** using KHMDS and LHMDS as a base.



Scheme 2. Preparation of (*R*)-α-amino carbonyl **6**.

This complementary amination process is applicable to various aryl-substituted substrates **1b**–**e**. Toward this end, good to high levels of stereoselectivities of the aminating adducts with *S* configuration (except for **2e** due to the priority numbering) were obtained, when **1b**–**e** were treated with KHMDS followed by the addition of di-*tert*-butyl azodicarboxylate (entries 7, 9, 11, and 13). The ^{1}H NMR signal of the corresponding C-5 methine proton in **2b**–**e** consistently appeared in a range of 3.50–3.62 ppm. On the other hand, reversal of stereoselectivity of the aminated adducts **3b**–**e** (*R* configuration, except for **3e**) was observed when LHMDS was used under the same conditions (entries 8, 10, 12, and 14). The ^{1}H NMR signal of the C-5 methine protons in **3b**–**e** appears in a range of 4.41–4.53 ppm as expected. The characteristic features of the ^{1}H NMR spectra of the hydrazides **2** and **3** permitted the assignment of the newly generated stereogenic centers. No reaction occurred when a bulky substituent **1f** (R = *t*-butyl) was used. To complete one cycle of the chiral auxiliary, the aminated adducts (*S*)-**2a** and (*R*)-**3a** were then subjected to reduction conditions. Exposure of **2a** to $NaBH_4$ in THF at ambient temperature provided the desired hydrazido alcohol (*S*)-**4** (65%) ($[\alpha]_D$ +34.5 (*c* 1.0, $CHCl_3$)), and camphor N^2-phenylpyrazolidinone was recovered in 84% yield (Scheme 1). Similar conditions were applied to give (*R*)-**4** ($[\alpha]_D$ −39.0 (*c* 1.0, $CHCl_3$)) with 82% yield, when **3a** was used.

The mechanistic explanation for the asymmetric amination has not yet been elucidated at this moment and can be rationalized by the structurally well-defined metal enolate geometries in the transition states as depicted in Figure 3.[9a] The hydrogen bond formed between the α-hydrogen and the carbonyl group of di-*tert*-butyl azodicarboxylate may play a role in stabilizing the favored enolate complexes. The eight-membered potassium *Z*-enolate is preferentially formed, when **1a** is treated with KHMDS to give the corresponding adduct **2a**. On the other hand, the six-membered lithium *E*-enolate is energetically favored, when LHMDS is used, resulting in the formation of **3a** as the major isomer. The size of the metal counterion may also be important in forming the eight-membered and six-membered enolates.

An interesting imino intermediate **5** was isolated, when the amination reaction was carried out at −78 °C followed by warm up to 0 °C gradually (Scheme 2). When phenylacetyl-substituted pyrazolidinone **1a** was treated with KHMDS and di-*tert*-butyl azodicarboxylate at −78 °C and warmed up to 0 °C over a period of 5 h, the imino product **5** was isolated with high chemical yield. On the other hand, when the reaction temperature was raised to −30 °C, hydrazide **2a** was isolated as the major product (70%), and the imino intermediate **5** was obtained with 20% chemical yield. Tributyltin hydride reduction of **5** in THF afforded the Boc-protected (*R*)-α-amino product **6** (70% de) as the major diastereomer in a total of 83% chemical yield. The hydride attacks from the bottom *si* face of the imino functionality in **5**.[12]

In conclusion, complementary metal enolate amination of the auxiliary-derived *N*-acyls was developed for the synthesis of two possible hydrazide diastereomers. Either isomer can be obtained with excellent chemical yield and high diastereoselectivity (up to 90% de), when aryl-substituted camphor N^1-acyl N^2-phenylpyrazolidinones are treated with KHMDS and LHMDS, respectively, followed by the addition of di-*tert*-butyl azodicarboxylate. This extends the synthetic applications to the versatile and general utility of camphor N^2-phenylpyrazolidinone as a good stereocontrolling element in diastereoselective reaction.

Acknowledgments

This work was supported by the National Science Council of the Republic of China (NSC 96-2113-M-003-005-MY3) and the National Taiwan Normal University (96TOP001). Our gratitude goes to the Academic Paper Editing Clinic, NTNU, and we are also grateful to the National Center for High-Performance Computing for computer time and facilities.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.003.

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10. Variable-temperature ^{1}H NMR studies of **2a** showed that the conformeric ratio increases with increasing temperature. For example, the conformeric ratio of hydrazide **2a** is 1.5 when the spectrum was recorded at −15 °C. The ratio was increased to 1.7 (at 5 °C), to 1.9 (at 25 °C) and further to 2.3 (at 55 °C). Interestingly, a third conformer appears when the temperature was decreased to −55 °C.
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12. The absolute stereochemistry of the minor (*S*)-α-amino diastereomer **6** was confirmed by single crystallographic X-ray analysis.