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Diastereoselective Michael reactions of (1*R*)-(+)-camphor methyl ketone enolates with nitro olefins

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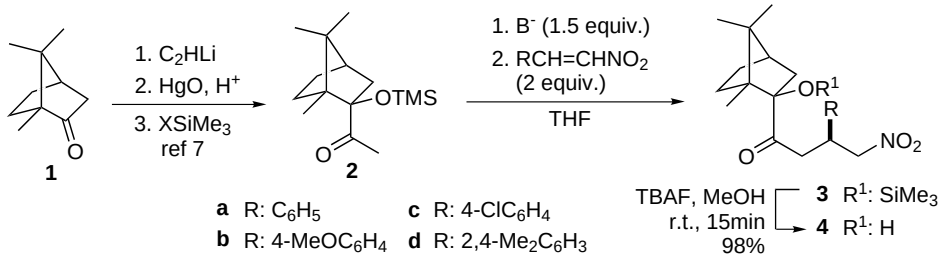
Abstract—The reaction of the sodium enolate of the methyl ketone **2** with a range of nitro olefins proceeds readily to give the corresponding Michael adducts in good yields and diastereoselectivities. Subsequent oxidative cleavage of the acyloin moiety provides γ-nitroalkanoic acids along with (1*R*)-(+)-camphor, the chiral auxiliary of the process, which can be recovered and reused.

The asymmetric Michael addition of enolizable carbonyl compounds to electron deficient olefins is a fundamental process for the stereoselective construction of C–C bonds.[1,2] Nitroalkenes are of special interest as powerful Michael acceptors due to the strong anion-stabilizing effect of the nitro group which causes the reaction to proceed with very high efficiency.[3] On the other hand, the nitro group can be transformed into other functionalities such as the carbonyl group via Nef reaction or an amino group by reduction.[4] However, despite the recent advances in this area,[5] there are very few examples of diastereoselective Michael reactions with nitro olefins.[6] One important problem associated with this process is the usual lack of stereoselection with enolates of α-unsubstituted carboxylic acid derivatives.[7] Recently we have reported on the use of the methyl ketone **2** in 'acetate' aldol[8] and Mannich[9] reactions. Herein we report on the reaction of **2** with aromatic nitro olefins[10] as the key-step for a highly stereoselective synthesis of γ-nitroalkanoic acids and their γ-lactam derivatives. These compounds are precursors of γ-amino acids which have potent activity on the central nervous system.[11]

As Scheme 1 illustrates, the methyl ketone **2**, readily available from (1*R*)-(+)-camphor **1** and acetylene,[8] upon treatment with NaHMDS and subsequent reaction with nitrostyrene in THF at −78°C provided the adduct **3a** in good yield and acceptable diastereoselectivity. Under similar reaction conditions, the lithium enolate of **2**, generated from either LDA or LiHMDS, worked without efficiency in terms of diastereoselectivity, and the potassium enolate of **2** did not provide the expected adduct. Results are listed in Table 1 to illus-



Scheme 1.

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Table 1. Diastereoselective Michael reactions of **2** with nitro olefins

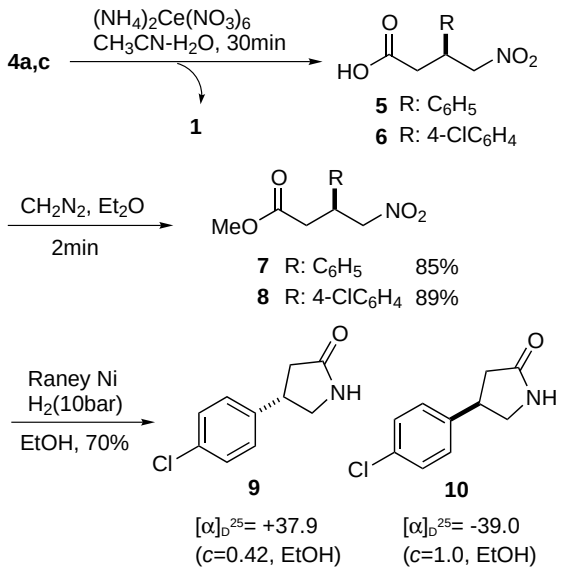
Product	Base	*t* (h)	d.r.[a]	Yield %[b]
3a	LDA	16	75:25	nd
	LiHMDS	0.5	70:30	nd
	NaHMDS	0.5	93:7	67
3b	LDA	16	65:35	nd
	NaHMDS	0.5	94:6	65
4c	NaHMDS	0.5	93:7	64[c]
4d	NaHMDS	0.5	94:6	53[c]

[a] Determined by ^{1}H NMR (500 MHz) and by HPLC (Lichorsorb Si 60, 5 μm, 20°C; eluant: ethyl acetate:hexane 1:99).
[b] Yield of isolated, pure products. nd: not determined.
[c] Overall from **2**.

trate the excellent diastereofacial selection observed for the reaction of the sodium enolate of **2** with some representative aromatic nitro olefins.

These adducts are of particular interest in that they provide, through oxidative cleavage of the acyloin moiety, γ-nitroalkanoic acids. For example, Scheme 2, compounds **5** and **6** were produced along with (1*R*)-(+)-camphor **1** by exposure of the adducts **4a** and **4c** to a threefold excess of ammonium cerium nitrate (CAN) in acetonitrile/water. From each crude mixture, the chiral auxiliary **1** was isolated by extraction with pentane in 95–97% yield[12] and the resulting γ-nitroalkanoic acids were isolated as their methyl esters **7** and **8** in 85 and 89% yields, over the two steps, respectively. The stereochemical assignments for the major products were established primarily by conversion of **8** into the γ-lactam **9**. The observed optical rotation of **9** was then compared with that of **10**. In addition, a single-crystal X-ray analysis of the Michael adduct **4c**[13] corroborated its assigned configuration.

In summary, we have developed a strategy for the asymmetric Michael reaction of an 'acetate' enolate equivalent with nitro olefins that formally involves the use of acetylene as the elementary source of carbonyl (acetyl) and (1*R*)-(+)-camphor as the source of chiral information. In addition, from an economical point of view, such a process with (1*S*)-(+)-camphor would also be viable as a route to the biologically active (*R*)-γ-amino acids, since the chiral controller, with no loss of chiral integrity, might be recovered at the final stage and could be reused.



Scheme 2.

Acknowledgements

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10. From the results in hand, it appears that the stereochemical outcome of the Michael addition process of the metal enolates of **2** with aliphatic nitro olefins differs from the aromatic cases, the lithium enolate being the best in terms of diastereoselectivity. These results will be published in due course.
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12. In each case, the recovered (1*R*)-(+)-camphor showed an optical rotation value of $[\alpha]_D^{25}=+41.5/+42.0$ ($c=1.0$, EtOH) ($[\alpha]_D^{25}=+42.2$ ($c=1.0$, EtOH) for the starting camphor, purchased from Aldrich).
13. The X-ray crystal structure analysis has been performed by one of us (A.L.) at the Organisch-chemisches Institut der Universität Zürich. Crystallographic data (excluding structure factors) for compound **4c** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 156554. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge, CB2, 1EZ, UK. E-mail: deposit@ccdc.cam.ac.uk.