Regio- and Diastereoselective Synthesis of β-Amino Ketones by Addition of Imines to Iminium Salts**

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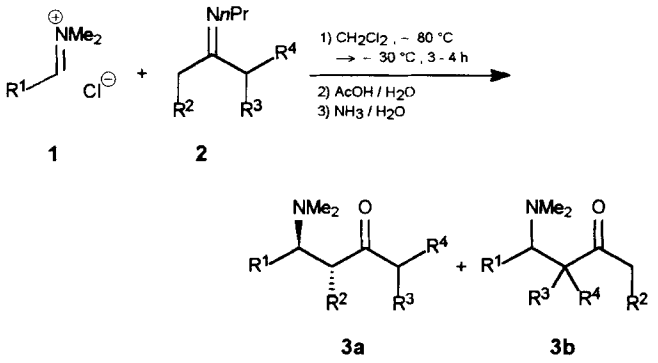
β-Amino ketones (Mannich bases) and their derivatives have a wide range of applications, for example in drugs, crop protection agents, and as general synthetic building blocks.[2] However, the Mannich reaction, the classical method of synthesizing β-amino ketones is fraught with many serious disadvantages—drastic reaction conditions, formation of undesired side products, little or no stereo- or regioselectivity, etc.[2] Numerous attempts have been made to overcome these limitations owing to the importance of the products.[3] Therefore, methods of stereoselective aminomethylation[4] and aminoalkylation[1, 5] are currently active areas of research.

In addition to controlling stereoselectivity, directing regioselectivity is a central, frequently unsolved problem in modern chemistry. Many attempts have been made to improve the regioselectivity of aminomethylation[3, 6] and thus simultaneously provide a versatile method for the regioselective functionalization of ketones (generation of Michael acceptors; the amino group can also be substituted readily).[2] The most important regioselective variants of the Mannich reaction are the reactions of methylene iminium salts with ketones,[6a] enolates, and enol ethers.[6b] However, these reactions either require tedious procedures, or their applications and efficiency have only limited known scope.

In comparison, the reaction of preformed iminium salts **1**[7] with imines **2** (Scheme 1) has fundamental advantages. The starting materials can be prepared readily from economical reagents or, like the methylene iminium salt **1** (R^1 = H), are commercially available. The preliminary, laborious regioselective synthesis of enolates or enol ethers is not necessary. This is not only a simple and convenient method, it also has a wide range of applications. The Mannich bases are prepared under mild conditions and obtained generally in analytically pure form in good yields and with excellent regioselectivities. In contrast to all other approaches, our method can also be used for regioselective amino*alkyl*ation, which is highly diastereoselective as well (Table 1).



Scheme 1. Regio- and diastereoselective aminoalkylation of imines **2** with iminium salts **1**.

Table 1. Regio- and diastereoselective aminoalkylation of imines **2** with iminium salts **1**.

Entry	R^1	R^2	R^3	R^4	**3a**:**3b** [a]	Yield [%]
1	Ph	Me	Me	H		75
2	Ph	$(CH_2)_3$		H	-	69
3	H	$(CH_2)_3$		Me	≥99: ≤1	76 [b]
4	Ph	$(CH_2)_3$		Me	≥99: ≤1	68 [c]
5	H	Me	Me	Me	≥99: ≤1	76
6	Ph	Me	Me	Me	≥99: ≤1	69 [d]
7	H	Me	*i*Pr	H	94: 6	72
8	Ph	Me	*i*Pr	H	≥99: ≤1	62
9	H	Me	Et	H	73: 27	71
10	Ph	Me	Et	H	75: 25	69 [e]
11	H	Ph	Me	H	≥99: ≤1	78
12	Ph	Ph	Me	H	81: 19	68

[a] The ratios of regio- and diastereoisomers were determined by ^1H and ^{13}C NMR spectroscopy. Unless specified otherwise the products are diastereomerically pure (≥ 99% *ds*). [b] Two diastereomers (*cis*/*trans* diastereomers relative to the α and α′ centers) are obtained in a ratio of 63:37. The relative configurations of the diastereomers could not yet be determined. [c] Two diastereomers are obtained in a ratio of 7:3; these are presumably *cis*/*trans* diastereomers relative to the α and α′ centers (cf. footnote [b]). The relative configurations of the diastereomers could not yet be determined. [d] If the reaction is conducted at 25 °C (2 h), regioisomeric products are obtained with a ratio (**3a**:**3b**) of ≥99: ≤1 (59% yield). [e] If the reaction is conducted at 25 °C (2 h), regioisomeric products are obtained with a ratio (**3a**:**3b**) of 73:27 (62% yield). Similar results were obtained in THF (73:27, 61%) and MeCN (74:26, 60%), and when the iminium tetrachloroaluminate salt was used instead of the chloride salt (76:24, 59%).

In analogy to the mechanisms previously proposed for reactions of imines with other electrophiles,[8] we assume that not the imines but rather the corresponding tautomeric secondary enamines react with the iminium salts. This hypothesis is supported by the finding that identical products are obtained regardless of whether the benzylidene iminium salt **1** with R^1 = Ph is treated with imines **2** (Table 1, Entries 1,2) or with the corresponding tertiary enamines (pyrrolidine derivatives).[1] Typically the reaction of iminium salts **1** (R^1 = alkyl, aryl) with enamines yields exclusively the *anti* Mannich bases.[1] For this reason and also based on NMR spectroscopic data, we have assigned the *anti* configuration to all the β-amino ketones formed in the reaction of **1** (R^1 = Ph) with **2**.

This reaction differs from related reactions, for example the alkylation of imines with Michael acceptors[8] and the aminomethylation of ketones with methylene iminium salts,[6a] in a number of respects. Whereas in these other reactions the more highly substituted α-C atom is generally attacked, in our

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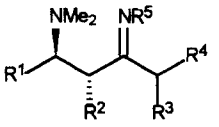
[**] Stereoselective Synthesis of Mannich Bases, Part 3. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. Part 2: ref. [1].

case the iminium salt attacks the sterically less hindered α position of the imine with high regioselectivity. Good regioselectivities are achieved even when the two α-C atoms are only marginally different (Table 1, cf. Entries 7 and 9, 8 and 10). Within the limits of our studies, the solvent, the counterion of the iminium salt, and the reaction temperature do not have a significant effect on the regio- and diastereoselectivity of the reaction (Table 1, footnotes [d] and [e]). The regioselectivity reversed, as expected, only when electronics dictate that the sterically more hindered tautomeric enamine is virtually the exclusive intermediate (Table 1, Entries 11, 12).



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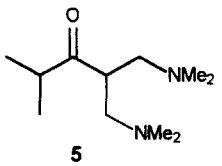
Besides these advantages the reaction of imines with iminium salts offers a list of notable prospects. The initially formed imines **4**, for example, are interesting synthetic building blocks, which may allow easy access to many valuable products (e.g. β-lactams and 1,3-diamines). Preliminary experiments also indicate that Mannich bases such as **5** can be obtained by bisaminomethylation with high regioselectivities and in good yields. Moreover, based on the excellent results achieved in the alkylation of chiral imines with Michael acceptors,[8] we expect our method to be suitable for the enantioselective synthesis of β-amino ketones.



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Experimental Procedure

3a: The reactions were conducted in water-free apparatus under argon. A solution of imine **2** (2.5 mmol) in anhydrous CH_2Cl_2 (2.5 mL) was cooled to −80 °C. The iminium salt **1** (2.5 mmol) was added in one portion and the reaction mixture was stirred for 3–4 h, during which the temperature increased to about −30 °C. To obtain good results in every case the reaction mixture should be stored for about 15 h at this temperature in a freezer before the workup. The reaction mixture was treated with aqueous AcOH solution (2 N, 5 mL) and Et_2O (50 mL), and stirred at 25 °C for 3–4 h. Then HCl (6 N, 5 mL) was added and the mixture stirred a further 10 min. The organic phase was decanted off and the aqueous phase washed with Et_2O (2 × 50 mL). The aqueous phase was finally treated with dilute NH_3 solution (25 mL, 25% NH_3:H_2O = 1:4) with vigorous stirring and extracted with Et_2O (3 × 50 mL, 1 min each). The combined organic phases were dried over Na_2SO_4 and the solvent removed on a rotary evaporator without heating.

Received: September 8, 1995 [Z8382IE]
German version: *Angew. Chem.* **1995**, *107*, 2861–2862

Keywords: aminoalkylations · asymmetric syntheses · imines · Mannich bases

[1] N. Risch, M. Arend, *Angew. Chem.* **1994**, *106*, 2531; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2422.
[2] M. Tramontini, *Synthesis* **1973**, 703; M. Tramontini, L. Angiolini, *Tetrahedron* **1990**, *46*, 1791.
[3] E. F. Kleinman in *Comprehensive Organic Synthesis, Vol. 2* (Eds.: B. M. Trost, C. H. Heathcock), Pergamon, Oxford, **1991**, p. 893; E. Winterfeldt, *J. Prakt. Chem.* **1994**, *336*, 91.
[4] N. Risch, A. Esser, *Liebigs Ann. Chem.* **1992**, 233.
[5] D. Seebach, M. Schiess, W. B. Schweizer, *Chimia* **1985**, *39*, 272; A. R. Katritzky, P. A. Harris, *Tetrahedron* **1990**, *46*, 987; E. G. Nolen, A. Allocco, M. Broody, A. Zuppa, *Tetrahedron Lett.* **1991**, *32*, 73; G. Oszbach, A. Neszmélyi, *Liebigs Ann. Chem.* **1990**, 211; M. R. Saidi, A. Heydari, J. Ipaktschi, *Chem. Ber.* **1994**, *127*, 1761.
[6] a) G. Kinast, L. F. Tietze, *Angew. Chem.* **1976**, *88*, 261; *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 239; Y. Jasor, M. Gaudry, M. J. Luche, A. Marquet, *Tetrahedron* **1977**, *33*, 295; b) J. Hooz, J. N. Bridson, *J. Am. Chem. Soc.* **1973**, *95*, 602; S. Danishefsky, M. Prisbylla, B. Lipisko, *Tetrahedron Lett.* **1980**, *21*, 805; S. Danishefsky, M. Kahn, M. Silvestri, *ibid.* **1982**, *23*, 1419; C. Rochin, O. Babot, J. Dunoguès, F. Duboudin, *Synthesis* **1986**, 667.
[7] N. Risch, M. Arend, *Methoden Org. Chem. (Houben-Weyl) 4th ed. 1952–, Vol. E21b* **1995**, p. 1925, and references therein.
[8] J. d'Angelo, D. Desmaële, F. Dumas, A. Guingant, *Tetrahedron Asymmetry* **1992**, *3*, 459; P. W. Hickmott in *The Chemistry of Enamines* (Ed.: Z. Rappoport), Wiley, Chichester, **1994**, p. 843, and references therein.

Asymmetric Sulfide Oxidation with Vanadium Catalysts and H_2O_2**

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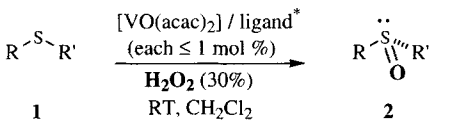
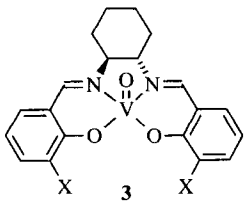
The evaluation of asymmetric catalytic reactions often fails to consider practical criteria important for applications in large-scale reactions.[1] Generally, attention is focused on the enantioselectivity and not on the practicability of the reaction or the catalytic efficiency, which is measured as the turnover number per time. There are only few enantioselective catalytic reactions that meet the expectations of the users and are therefore employed in syntheses by people both outside and inside the research groups originally involved in their development.[2] We report herein a method for the asymmetric oxidation of sulfides,[3] which provides optically active sulfoxides with *ee* values up to 85%. Moreover, this method proceeds under very simple reaction conditions (room temperature, exclusion of air and humidity unnecessary) and can be performed with H_2O_2, a cheap and safe oxidizing agent, as well as with a readily accessible chiral vanadium catalyst (≤ 1 mol%) [Eq.(a)].



1 **2** (a)

Enantioselective oxidations of aryl alkyl sulfides with vanadium complexes were reported by Fujita and co-workers as early as 1986. Using 10 mol% of the vanadium–salen catalyst **3** and cumyl hydroperoxide as the oxygen source, they obtained enantioselectivites of up to 40% *ee*.[4–6] The enantioselectivities reported by Fujita et al. are lower than those obtained when using



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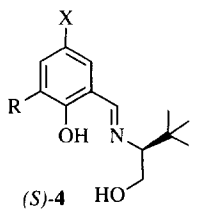
X = OMe, OEt, *t*Bu



(S)-**4**

a: R = *t*Bu, X = NO_2
b: R = X = *t*Bu
c: R = $SiPh_2$*t*Bu, X = *t*Bu
d: R = H, X = NO_2

the modified Sharpless reagent [tartrate, $[Ti(OiPr)_4]$, H_2O, organic hydroperoxide],[7] which was introduced by Kagan et al. for the oxidation of sulfides. Nevertheless, the vanadium-catalyzed transformation has the advantage of requiring a smaller amount of the carrier of chiral information (metal and ligand).

We have now found that sulfides can be oxidized rapidly and efficiently into optically active sulfoxides (ee_{max} = 85%) by us-

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[**] This work was supported by the Deutsche Forschungsgemeinschaft (Schwerpunktprogramm: Sauerstofftransfer/Peroxidchemie, Graduierten-Kolleg). We thank the BASF for a doctoral stipend (F. B.) and the Degussa for the donation of chemicals.