Synthesis of a Ketorolac Model *via* Aromatic Carbenoid Insertion

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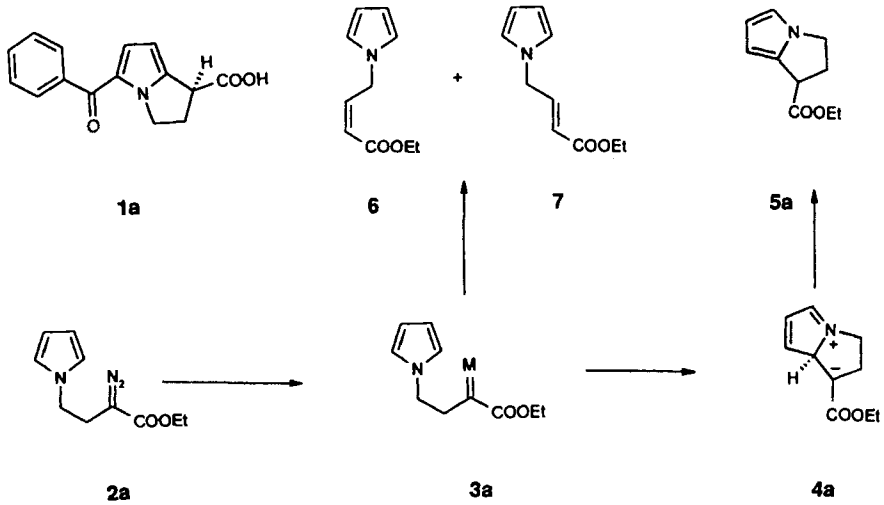
The decomposition of diazo ester **2b** with chiral Rh^{II} catalysts proceeded *via* intramolecular aromatic carbenoid insertion to the racemic pyrrole derivative **5b** in 72% yield. In contrast, the benzoylated precursor **16** afforded no ketorolac **1b** when exposed to Rh^{II}. Methyl 2-diazo-4-phenylbutyrate (**19**), in turn, reacted, by 1,2-hydrogen migration rather than by aromatic substitution, to **20**.

Introduction. – Ketorolac (= 5-benzoyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic acid; **1a**), is a highly potent and antiinflammatory analgesic, which has found applications in areas of pain therapy usually reserved for opiates [1]. The classical synthetic approaches to racemic ketorolac (**1a**) involve intramolecular nucleophilic displacement reactions of appropriately *N*,2-disubstituted 5-aroyl-pyrroles. The pharmaceutically active (–)-(*S*)-isomer of **1a** was obtained by resolution of the racemate *via* the chinchonidine and chinchonine salt [2]. Synthesis of ketorolac by a carbenoid ring closure has also been attempted, albeit with very limited success [3]. Decomposition of the diazo ester **2a** with Cu^{I} catalysts in hydrocarbon solvents afforded the unsubstituted ketorolac ester **5a** in yields of 7–15%, according to the reaction conditions. The main products were the (*Z*)- and (*E*)-olefins **6** (17–28%) and **7** (13–51%), which arise from 1,2-H migration of the intermediate metal carbenoid **3a** (*Scheme 1*).

Scheme 1



Aromatic substitution of pyrroles *via* transition-metal-catalyzed diazo decomposition has been known for some time [4]. Mechanistically, the reaction is analogous to the insertion of carbenes into C,H bonds of aromatic hydrocarbons. This formal insertion proceeds *via* an electrophilic aromatic substitution [5]. It differs mechanistically from the carbene insertion into aliphatic C,H bonds which proceeds in a single step with retention of configuration at the reacting C-atom [6]. With pyrroles, a zwitterion **4a**, stabilized by the lone pair of the N-atom has been proposed as reactive intermediate.

The intramolecular metal-catalyzed cyclization of terminal diazo ketones has been applied to the synthesis of a variety of pyrrole and indole derivatives [7], and enantiomerically pure (−)-indolizidine 167B and (+)-monomerine have been synthesized by the same approach from optically active precursors [8]. In these sequences, the intermediate carbenoids have the carbenic center separated from the aliphatic chain by a C=O group, so that of competing 1,2-H migration leading to olefins, which is detrimental in the case of ketorolac (**1a**), may not intervene.

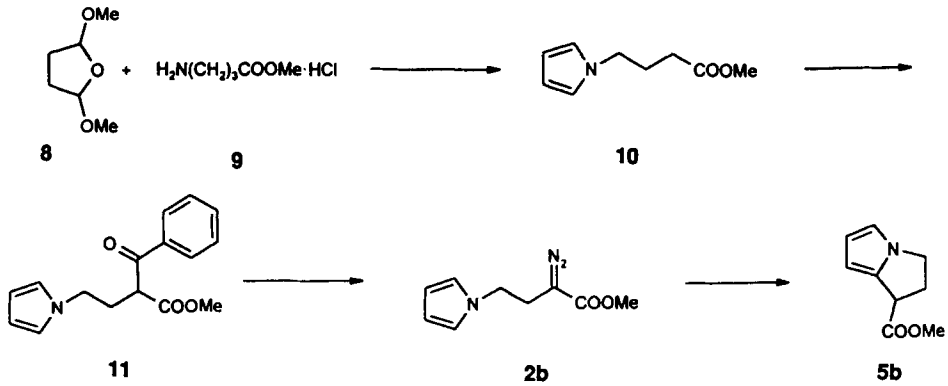
Since the C-atom carrying the diazo group of the ketorolac precursor **2a** carries two different substituents, the C,H insertion of the carbene results in generation of a chiral center. In principle, the use of a chiral catalyst may afford optically active **5a**. However, to our knowledge, an asymmetric carbenoid insertion into an aromatic C,H bond has not yet been realized. An example of an enantioselective aromatic C,H insertion has been reported, but there the selection occurred between two enantiotopic Ph groups, and the carbenic center did not become chiral [9].

The carbenoid synthesis of ketorolac (**1a**) presents two problems to overcome, namely the chemoselectivity between intramolecular aromatic substitution and 1,2-H migration on one side, and the asymmetric induction upon insertion into aromatic C,H bonds on the other. Since the selectivity of metal-catalyzed diazo decompositions is strongly dependent upon the metal, the ligand associated with it, and upon the solvent [10], we expected that an appropriate choice of catalyst and reaction conditions would allow to direct the reaction to the desired product. In view of our interest in asymmetric carbenoid reactions [11], we have reinvestigated the synthesis of ketorolac (**1a**) and that of *Muchowski*'s model compound **5a**.

Results and Discussion. – Our synthesis of the diazo precursor **2b** starts with 2,3,4,5-tetrahydro-2,5-dimethoxyfuran (**8**) which was condensed with methyl 4-aminobutyrate (**9**) according to the procedure of *Jefford et al.* [12] to afford the pyrrol-1-yl derivative **10** in 73% yield (*Scheme 2*). The desired diazo compound **2b** was obtained *via* benzoylation to **11** (PhCOOMe/NaH, 38%) followed by diazo transfer (NsN_3, DBU (= 1,8-diazabicyclo[5.4.0]undec-7-ene), 70%) [13]. Decomposition of **2b** at room temperature in CH_2Cl_2 in the presence of $[Rh_2\{(2S)\text{-mepy}\}_4]$ [14] afforded the cyclization product **5b** in 72% yield. No olefins derived from 1,2-H migration were detected in the reaction mixture. Apparently, the change from Cu- to Rh^{II}-based catalysts is sufficient to change the selectivity of the carbene in favor of aromatic substitution. However, the product of the reaction catalyzed with $[Rh_2\{(2S)\text{-mepy}\}_4]$ was racemic. Similarly, only racemic **1b** was isolated when the reaction was carried out with $[Rh_2\{(4S)\text{-phox}\}_4]$ [15].

The absence of asymmetric induction in this diazo decomposition may be due to a variety of causes, such as an inappropriate choice of catalyst, or to racemization of the cyclized product, problems which might eventually be overcome by modification of the

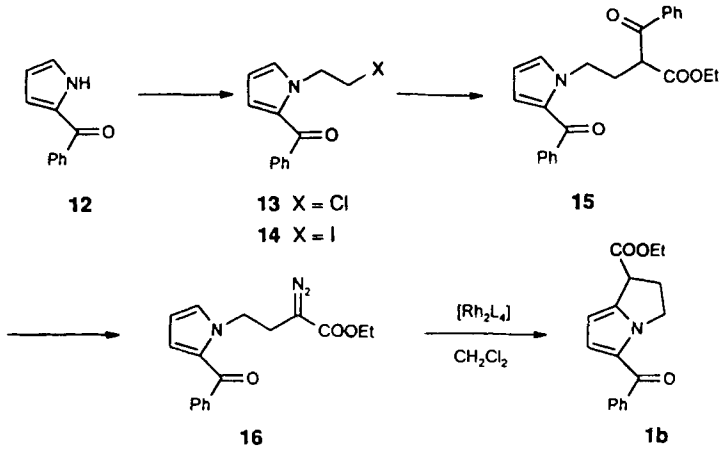
Scheme 2



reaction conditions. Even if the attack of the metallocarbene occurs selectively on one of the enantiotopic faces of the pyrrole ring, loss of stereochemistry may occur during the transfer of the proton in the presumed zwitterionic intermediate **4a** to the carbenic center. The structure of this zwitterion, in particular its association with the metal, and the details of the mechanism of the proton transfer are unknown. Concievably, the life-time of the intermediate may be modified by substituents on the heterocyclic ring or on the C=O group, and appropriate substitution may help to control the stereochemical course of the proton transfer.

Application of the carbenoid cyclization to the substituted ketorolac ester **1b** was not possible, however. The benzoylated precursor was synthesized from 2-benzoylpyrrole (**12**) [16] which was alkylated with 1,2-dichloroethane, under phase-transfer conditions [17], to yield 2-benzoyl-*N*-(2-chloroethyl)pyrrole (**13**) (*Scheme 3*). The Cl-group of **13** was exchanged by reaction with NaI in refluxing MeCN [18], and the resulting iodide **14** was displaced by reaction with ethyl benzoylacetate to afford the keto ester **15** in poor

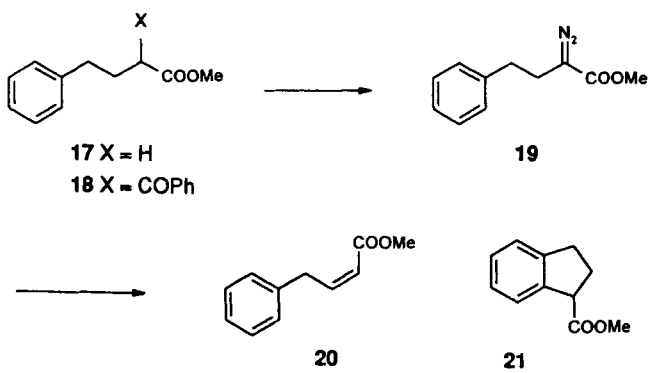
Scheme 3



yield (10–15%). The diazo compound **16** was formed in 56% yield upon reaction of **15** with NsN_3 in the presence of DBU. Exposure of **16** to $[Rh_2(OAc)_4]$ in CH_2Cl_2 at room temperature resulted in decomposition of the starting material to form an untractable mixture of products in which the desired ketorolac derivative **1b** could not be detected. When $[Rh_2\{(2S)\text{-mepy}\}_4]$ was used as catalyst, no reaction took place at room temperature, but decomposition to an equally complicated mixture occurred at reflux.

The failure of the ketorolac precursor **16** to undergo intramolecular cyclization may be attributed to the electron-withdrawing nature of the PhCO substituent. A decrease in electron density of the heterocyclic ring reduces its reactivity towards electrophilic substitution so that secondary reactions such as H migration or formation of carbene dimers become competitive. To back up this hypothesis the Ph substituted diazo ester **19** was synthesized by benzoylation of methyl 4-phenylbutyrate (**17**) with PhCOOMe/NaH, followed by diazo transfer of the resulting keto ester **18** (*Scheme 4*). Decomposition of **19** with $[Rh_2(2S)\text{-mepy}\}_4]$ afforded only the (*Z*)-configurated unsaturated ester **20** [19] (63%), and no product resulting from intramolecular aromatic substitution **21** could be detected. The absence of **21** is consistent with the lower reactivity of the benzene ring in comparison to the pyrrole in electrophilic substitutions [20]. The formation of **19** having (*Z*)-configuration in preference over the thermodynamically more stable (*E*)-isomer is a common phenomenon in Rh^{II}-catalyzed diazo decompositions involving 1,2-H migration [21].

Scheme 4



The present experiments show that ketorolac (**1a**) may be accessible *via* intramolecular carbenoid cyclization if the pyrrole ring is not deactivated towards electrophilic substitution by electron-withdrawing substituents. The realization of an enantioselective synthesis of **5a** *via* aromatic carbenoid C,H insertion, and the enantioselective aromatic C,H insertion in general, however, will require more extensive investigations, which are in progress in our laboratory.

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Experimental Part

General. See [22].

*Methyl 1,2-Dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylate* (**5b**). *Methyl 4-(Pyrrol-1-yl)butyrate* (**10**). To *methyl 4-aminobutyrate hydrochloride* (**9**; 3.07 g, 20 mmol) in H_2O (30 ml) were added, successively, AcONa (1.64 g, 1.0 equiv.), AcOH (10 ml), 1,2-dichloroethane (30 ml), and 2,5-dimethoxytetrahydrofuran (2.64 g, 20 mmol). The heterogeneous mixture was heated to 80° with vigorous stirring during 45 min. After cooling, the layers were separated; the aq. layer was extracted several times with CH_2Cl_2, dried ($MgSO_4$), and evaporated. The crude product was purified with silica gel (hexane/Et_2O 1:1): 2.40 g (73%) of **10**. Oil. IR (CH_2Cl_2): 3054*m*, 2954*s*, 1734*s*, 1500*s*, 1438*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 6.65–6.63 (*m*, 2 H); 6.16–6.13 (*m*, 2 H); 3.94 (*t*, *J* = 6.6, 2 H); 3.68 (*s*, 3 H); 2.33–2.25 (*m*, 2 H); 2.17–2.00 (*m*, 2 H). ^{13}C-NMR: 173.2 (*s*); 120.5 (*d*); 108.2 (*d*); 51.6 (*q*); 48.4 (*t*); 30.7 (*t*); 26.7 (*t*). MS: 167 (100, M^+), 150 (11), 136 (55), 108 (13), 94 (27), 93 (20), 81 (60), 80 (55), 67 (10), 53 (16). HR-MS: 167.0955 ($C_9H_{13}NO_2^+$; calc.: 167.0946).

Methyl 2-Benzoyl-4-(pyrrol-1-yl)butyrate (**11**). To NaH (0.92 g, 23 mmol), suspended in DME (20 ml), **10** (960 mg, 5.8 mmol) in DME (2.0 ml) was added at 0°. After 10 min at 10°, methyl benzoate (1.19 g, 8.7 mmol) in DME (2.0 ml) was added. The mixture was heated to reflux during 8 h. After cooling, it was neutralized with 1N HCl to pH 4. The org. phase was extracted twice with Et_2O (20 ml), dried ($MgSO_4$), and evaporated. The crude product was purified by CC (silica gel; AcOEt/hexane 1:10): 0.60 g (38%) of **11**. Oil. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.85–7.40 (*m*, 5 H); 6.61–6.59 (*m*, 2 H); 6.18–6.16 (*m*, 2 H); 4.18 (*t*, *J* = 7.2, 1 H); 4.00 (*t*, *J* = 6.4, 2 H); 3.69 (*s*, 3 H); 2.50–2.35 (*m*, 2 H). ^{13}C-NMR: 194.6 (*s*); 169.9 (*s*); 135.5 (*s*); 133.7 (*d*); 128.8 (*d*); 128.7 (*d*); 120.6 (*d*); 108.6 (*d*); 52.6 (*q*); 50.2 (*d*); 47.0 (*t*); 30.8 (*t*). MS: 271 (15, M^+), 254 (4), 205 (5), 191 (5), 105 (60), 93 (100), 81 (30), 80 (30), 77 (45), 53 (25). HR-MS: 271.1208 ($C_{16}H_{17}NO_3^+$; calc.: 271.1208).

Methyl 2-Diazo-4-(pyrrol-1-yl)butyrate (**2b**). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU; 0.30 ml, 2.0 mmol) was added to **11** (260 mg, 0.95 mmol) in CH_2Cl_2 (2.0 ml) at 0°. After 10 min, NsN_3 (466 mg, 2.0 mmol) in CH_2Cl_2 (2.0 ml) was added. The temp. was allowed to rise to 20° with stirring within 30 min. Phosphate buffer (pH 7.0); 3.0 ml, 0.5M and H_2O (4.0 ml) were added. The layers were separated, and the aq. phase was washed with 3 portions of CH_2Cl_2 (10 ml). After drying ($MgSO_4$) and evaporation of the org. phase, the crude material was purified by CC (silica gel; AcOEt/hexane 1:10): 0.13 g (70%) of **2b**. Yellow oil. IR (CH_2Cl_2): 3054*w*, 2954*w*, 2090*s*, 1690*s*, 1498w, 1438*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 6.64–6.61 (*m*, 2 H); 6.18–6.16 (*m*, 2 H); 4.04 (*t*, *J* = 6.4, 2 H); 3.78 (*s*, 3 H); 2.70 (*t*, *J* = 6.4, 2 H). ^{13}C-NMR: 167.4 (*s*); 120.4 (*d*); 108.9 (*d*); 52.0 (*q*); 47.7 (*t*); 27.1 (*t*). MS: 165 (18, $[M-28]^+$), 150 (59), 106 (60), 80 (100), 53 (64). HR-MS: 165.0799 ($C_9H_{11}NO_2^+$; calc.: 165.0789).

Compound **5b**. Compound **2b** (193 mg, 1.00 mmol) in freshly distilled CH_2Cl_2 (5.0 ml) was added unter N_2 during 20 h by means of a syringe pump to CH_2Cl_2 (20 ml) containing [Rh_2{(2*S*)-mepy}$_4$] (20 mg, 0.02 mmol). After the addition, the catalyst was removed by filtration through a plug of silica gel. The solvent was evaporated and the residue purified by CC (silica gel; CH_2Cl_2/hexane 3:2) to afford 120 mg (72%) of **5b**. IR (CH_2Cl_2): 2954*m*, 1736*s*, 1436*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 6.64–6.61 (*m*, 1 H); 6.25–6.22 (*m*, 1 H); 6.00–5.97 (*m*, 1 H); 4.18–4.09 (*m*, 1 H); 4.07–3.92 (*m*, 2 H); 3.74 (*s*, 3 H); 2.90–2.82 (*m*, 1 H); 2.79–2.68 (*m*, 1 H). ^{13}C-NMR: 172.7 (*s*); 133.6 (*s*); 114.5 (*d*); 112.6 (*d*); 100.6 (*d*); 52.2 (*q*); 45.4 (*t*); 42.1 (*d*); 31.4 (*t*). MS: 165 (33, M^+), 106 (100), 104 (15), 79 (20), 51 (8). HR-MS: 165.0796 ($C_9H_{11}NO_2^+$; calc.: 165.0790).

Attempted Synthesis of Ketorolac Ester **1b**. *2-Benzoyl-*N*-(2-chloroethyl)pyrrole* (**13**). *2-Benzoylpyrrole* (**12**) was alkylated with 1,2-dichloroethane according to the procedure of *Muchowski* [18] to afford **13** in 75% yield. M.p. 54°. IR (CH_2Cl_2): 1626*s*, 1527*w*, 1466*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.82–7.78 (*m*, 2 H); 7.60–7.40 (*m*, 3 H); 7.09–7.07 (*m*, 1 H); 6.84–6.80 (*m*, 1 H); 6.23–6.19 (*m*, 1 H); 4.69 (*t*, *J* = 5.7, 2 H); 3.94 (*t*, *J* = 5.7, 2 H). ^{13}C-NMR: 186.2 (*s*); 139.7 (*s*); 132.2 (*d*); 131.5 (*d*); 129.5 (*d*); 129.1 (*d*); 128.1 (*d*); 124.1 (*d*); 108.4 (*d*); 51.3 (*t*); 44.5 (*t*). MS: 233 (29, M^+), 198 (80), 156 (10), 105 (100), 94 (36), 77 (55), 51 (18). HR-MS: 233.0601 ($C_{13}H_{12}NO^{35}Cl^+$; calc.: 233.0607).

*2-Benzoyl-*N*-(2-iodoethyl)pyrrole* (**14**). The chloride **13** (2.75 g, 11.8 mmol) was heated in MeCN (200 ml) with NaI (3.53 g, 23.6 mmol) to reflux for 48 h. The soln. was cooled and concentrated. After extraction with AcOEt, the org. layer was washed (H_2O), dried ($MgSO_4$), and concentrated under reduced pressure. Crude **14** was purified by CC (silica gel; hexane/AcOEt 85:15) to afford 1.90 g (51%) of **14**. A viscous, red liquid. ^{1}H-NMR ($CDCl_3$): 7.70–7.64 (*m*, 2 H); 7.38–7.30 (*m*, 3 H); 6.91–6.89 (*m*, 1 H); 6.68–6.66 (*m*, 1 H); 6.09–6.07 (*m*, 1 H); 4.57 (*t*, *J* = 6.9, 2 H); 3.44 (*t*, *J* = 6.9, 2 H). ^{13}C-NMR: 186.0 (*s*); 139.7 (*s*); 131.6 (*d*); 131.3 (*d*); 129.4 (*s*); 129.2 (*d*); 128.1 (*d*); 124.0 (*d*); 108.5 (*d*); 51.8 (*t*); 5.1 (*t*). MS: 325 (52, M^+), 198 (83), 105 (100), 94 (48), 77 (70), 51 (34). HR-MS: 324.9970 ($C_{13}H_{12}ONI^+$; calc.: 324.9963).

Ethyl 2-Benzoyl-4-(2-benzoylpyrrol-1-yl)butyrate (**15**). To ethyl 2-benzoylacetate (13.0 g, 67.6 mmol) in anh. DMF (50 ml), NaH (60% suspension, 1.35 g, 33.8 mmol) was added at 0°. The mixture was stirred at r.t. during

30 min, whereupon **14** (11.0 g, 33.8 mol) in DMF (50 ml) was added. The mixture was stirred during 24 h at r.t. It was then poured into H_2O (1000 ml), which was extracted with AcOEt (3 × 300 ml). The org. phase was washed with H_2O (2 × 200 ml) and sat. NaCl (300 ml). After drying ($MgSO_4$) and evaporation under reduced pressure, the crude product was subjected to CC (silica gel; hexane/AcOEt 85:15) to yield **15** (2.20 g, 16%). IR (CH_2Cl_2): 3046*w*, 2982*w*, 1736*s*, 1687*m*, 1627*s*, 1598*m*, 1525*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): 8.05–7.40 (*m*, 10 H); 7.00–6.96 (*m*, 1 H); 6.77–6.73 (*m*, 1 H); 6.20–6.17 (*m*, 1 H); 4.55 (*t*, *J* = 6.9, 2 H); 4.38 (*t*, *J* = 7.0, 1 H); 4.15 (*q*, *J* = 7.1, 2 H); 2.52 (*m*, 2 H); 1.17 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR: 194.6 (*s*); 186.0 (*s*); 169.5 (*s*); 140.0 (*s*); 135.7 (*s*); 133.6 (*d*); 131.3 (*d*); 131.0 (*d*); 129.7 (*s*); 129.1 (*d*); 128.7 (*d*); 128.0 (*d*); 123.7 (*d*); 108.6 (*d*); 61.6 (*t*); 51.2 (*d*); 47.2 (*t*); 30.7 (*t*); 14.0 (*q*). MS: 389 (0.8, M^+), 197 (17), 184 (10), 105 (100), 91 (20), 77 (60), 51 (12). HR-MS: 389.1620 ($C_{24}H_{23}O_4N^+$; calc.: 389.1627).

Ethyl 4-(2-Benzoylpyrrol-1-yl)-2-diazobutyrate (**16**). DBU (0.15 ml, 1.0 mmol) was added to **15** (160 mg, 0.40 mmol) in CH_2Cl_2 (1.0 ml) at 0°. After 10 min, NsN_3 (230 mg, 1.0 mmol) in CH_2Cl_2 (1.0 ml) was added. The mixture was stirred at r.t. during 30 min. Phosphate buffer (pH 7.0, 0.5M, 1.5 ml) and H_2O (2.0 ml) were added and the layers separated. The aq. phase was extracted (CH_2Cl_2, 3 × 10 ml), and the org. phase dried ($MgSO_4$) and concentrated. CC (AcOEt/hexane 1:10) gave 70 mg (56%) of **16**. Yellow oil. IR (CH_2Cl_2): 3050*w*, 2984*m*, 2089*s*, 1732*m*, 1685*s*, 1626*s*, 1576*m*, 1525*m*, 1466*m*, 1400*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.80–7.70 (*m*, 2 H); 7.55–7.40 (*m*, 3 H); 6.95–6.93 (*m*, 1 H); 6.79–6.77 (*m*, 1 H); 6.21–6.19 (*m*, 1 H); 4.56 (*t*, *J* = 6.4, 2 H); 4.21 (*q*, *J* = 7.1, 2 H); 2.83 (*t*, *J* = 6.4, 2 H); 1.26 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR: 186.0 (*s*); 171.1 (*s*); 167.1 (*s*); 139.8 (*s*); 131.4 (*d*); 131.1 (*d*); 129.5 (*s*); 129.1 (*d*); 128.0 (*d*); 124.1 (*d*); 198.7 (*d*); 60.8 (*t*); 47.8 (*t*); 26.7 (*t*); 14.5 (*q*). MS: 283 (10, $[M-28]^+$), 254 (30), 210 (40), 178 (25), 150 (7), 105 (100), 91 (38), 77 (42), 51 (10). HR-MS: 283.1215 ($C_{17}H_{17}O_3N^+$; calc.: 283.1208).

Synthesis and Decomposition of Methyl 2-Diazo-4-phenylbutyrate (**19**). *Methyl 2-Benzoyl-4-phenylbutyrate* (**18**). To NaH (0.92 g, 23 mmol) in DME (20 ml), *methyl 4-phenylbutyrate* [23] (**17**; 1.02 g, 7.76 mmol) in DME (2.0 ml) was added at 0°. After 10 min at 0°, methyl benzoate (1.19 g, 8.7 mmol) in DME (2.0 ml) was added. The mixture was heated to reflux during 8 h. After cooling, 1N HCl was added until pH 4. The org. phase was separated, and the aq. layer was extracted with Et_2O (2 × 20 ml). After drying ($MgSO_4$) and evaporation of the org. phase, the residue was purified by CC (silica gel; AcOEt/hexane 1:10) to yield 1.04 g (64%) of **18**. Colorless liquid. IR (CH_2Cl_2): 3058*m*, 2954*m*, 1742*s*, 1686*s*, 1597*m*, 1496*m*, 1448*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.89–7.12 (*m*, 10 H); 4.31 (*d*, *J* = 7.0, 1 H); 3.68 (*s*, 3 H); 2.75–2.64 (*m*, 2 H); 2.40–2.25 (*m*, 2 H). ^{13}C-NMR: 195.0 (*s*); 170.3 (*s*); 140.6 (*s*); 135.9 (*s*); 133.5 (*d*); 128.7 (*d*); 128.5 (*d*); 128.4 (*d*); 126.2 (*d*); 52.8 (*q*); 52.4 (*d*); 33.4 (*t*); 30.5 (*t*). MS: 282 (1, M^+), 178 (95), 146 (32), 105 (100), 91 (23), 77 (63), 65 (12). HR-MS: 282.1270 ($C_{18}H_{18}O_3^+$; calc.: 282.1255).

Compound **19**. DBU (0.3 ml, 2.0 mmol) was added to **18** (268 mg, 0.95 mmol) in CH_2Cl_2 (2.0 ml) at 0°. After 10 min, NsN_3 (466 mg, 2.0 mmol) in CH_2Cl_2 (2.0 ml) was added. The mixture was stirred at r.t. during 30 min. After addition of phosphate buffer (pH 7.0, 0.5M, 3.0 ml) and H_2O (4.0 ml), the org. layer was separated, and the aq. phase extracted with CH_2Cl_2 (3 × 10 ml). After drying ($MgSO_4$) and concentration of the org. phase, the crude product was purified by CC (silica gel; AcOEt/hexane 1:10) to give **19** (170 mg, 86%). Yellow oil. IR (CH_2Cl_2): 3054*w*, 2953*w*, 2085*s*, 1690*s*, 1438*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.35–7.20 (*m*, 5 H); 3.75 (*s*, 3 H); 2.88–2.79 (*m*, 2 H); 2.64–2.55 (*m*, 2 H). ^{13}C-NMR: 167.7 (*s*); 140.1 (*d*); 126.4 (*d*); 51.8 (*q*); 33.9 (*t*); 25.4 (*t*). MS: 176 (28, $[M-28]^+$), 161 (11), 144 (30), 133 (15), 116 (32), 117 (55), 116 (32), 115 (69), 105 (10), 91 (100), 77 (10), 65 (29). HR-MS: 176.0834 ($C_{11}H_{12}O_2^+$; calc.: 176.0837).

Methyl (Z)-4-Phenylbut-2-enoate (**20**). Compound **19** (204 mg, 1.0 mmol) in freshly distilled CH_2Cl_2 (5.0 ml) was added, under N_2, in 20 h, by means of a syringe pump, to CH_2Cl_2 (20 ml), containing [Rh_2{(2*S*)-mepy}$_4$] (20 mg, 0.02 mmol). After the addition, the catalyst was removed by filtration through silica gel. The solvent was evaporated and the residue subjected to CC (silica gel; AcOEt/hexane .1:10): 111 mg (63%) of **20** [19]. IR (CH_2Cl_2): 3062*w*, 2952*w*, 1719*s*, 1646*m*, 1495*w*, 1438*m*, 1208*s*, 1170*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.35–7.24 (*m*, 5 H); 6.38 (*dt*, *J* = 11.6, 6.9, 1 H); 5.90 (*d*, *J* = 11.6, 1 H); 4.05 (*d*, *J* = 6.9, 2 H); 3.78 (*s*, 3 H). ^{13}C-NMR: 166.8 (*s*); 148.3 (*d*); 139.4 (*s*); 128.6 (*d*); 126.4 (*d*); 119.5 (*d*); 51.2 (*q*); 35.1 (*t*).

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