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High pressure activation in the asymmetric Michael addition of chiral imines to alkyl and aryl crotonates

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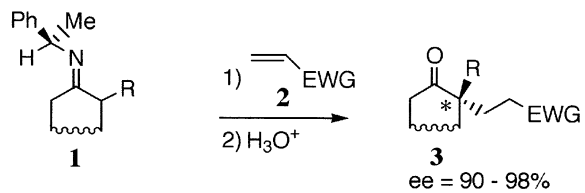
Abstract—High pressure-mediated Michael addition of chiral imines derived from 2-methylcyclopentanone, 2-methylcyclohexanone and optically active 1-phenylethylamine, to methyl and phenyl crotonates was investigated. The corresponding adducts were obtained in fair yields and with a high degree of regio-, diastereo- and enantioselectivity.

Owing to the widespread presence of quaternary carbon centers (QCCs) in natural products (e.g. terpenes, steroids, alkaloids), their elaboration remains a central challenge of contemporary organic synthesis.[1] However, several difficulties are encountered in constructing QCCs, particularly a severe steric hindrance, source of repulsion in the transition states which substantially increases their energy levels. Another peculiar aspect of QCCs is that their configurations are in most cases definitively secured by the mechanism-based stereoselectivity (kinetic control), racemization/epimerization at a QCC requiring the transient breaking of a C–C bond, of high dissociation energy values.[2] A conventional strategy for controlling sterically a QCC takes advantage of preexisting stereocenters in the starting substrate (substrate control principle). In the past two decades, several methods have been developed for the enantioselective generation of *individual* QCC, which involve the use of a chiral auxiliary or a chiral reagent/chiral catalyst (reagent control principle) to create a temporary chiral environment. In this respect, the asymmetric Michael reaction using chiral imines under neutral conditions we disclosed in 1985 has emerged as a simple and efficient tool for the stereocontrolled construction of individual QCC.[3] Thus, condensation of chiral imines **1**, derived from racemic 2-substituted cyclanones and enantiopure 1-phenylethylamine, to electron-deficient alkenes **2** furnished after hydrolytic workup 2,2-disubstituted cyclanones **3**, obtained in fair yields and with a high degree of regio- and stereoselectivity (Scheme 1).



Scheme 1.

A great variety of substrates have been used successfully in this Michael reaction, without alteration of its remarkable features. Regarding the electrophilic partner, not only a wide range of electron-withdrawing groups (COR, CO_2R, CN, SO_2Ph, NO_2), but also of α-substituents (alkyl groups, OAc, NHAc, SPh, Cl) can be employed. In contrast, β-substituted electrophilic alkenes turned out to be strongly deactivated acceptors, compared to their unsubstituted counterparts. Thus, for example, all attempts at condensing imine **4b** with methyl crotonate under standard thermal conditions failed.[4] To circumvent this vexing drawback, an alternative was found, which utilizes very reactive acceptors, such as crotonyl cyanide,[5] maleic anhydride,[6a–e] citraconic anhydride,[6b,c,e] phenyl crotonate[7] and 1-nitropropene.[8] However, although generally highly regio- and stereoselective, these additions were in most cases complicated by a subsequent *N*-heterocyclization of the primary adducts. Another striking feature of the croto-

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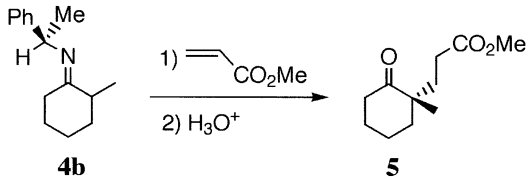
nate-type acceptors is that their reactivity was restored in the *intramolecular variants* of this conjugate addition: spiroannulation,[9] carbocyclization[10] and bridging annulation.[11] In such processes, a favorable entropic factor clearly counterbalances the steric hindrance.

As a part of our program directed at exploring the scope of this asymmetric Michael addition, and in connection with synthetic applications, we recently envisioned to reinvestigate the reactivity of alkyl and aryl crotonates, with the assistance of high pressure (HP)[12] to overcome the steric inhibition. The effect of pressure on reaction rates is given by the Evans–Polanyi equation:

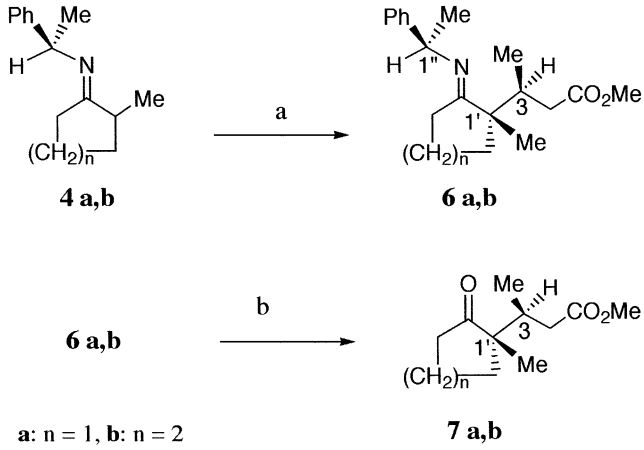
$$(\partial \ln k/\partial P)_T = -\Delta V^{\neq}/RT$$

where $\Delta V^{\neq}$ is the difference in partial molar volumes between reagents and transition states. This equation predicts an increase in rate if the transition state occupies a smaller volume than the total volume of reagents. Since steric crowding is usually associated with lower partial volumes, the application of HP sometimes permits the reactions to occur which are otherwise prevented by steric factors. In this respect, we have demonstrated in a series of preliminary experiments that the addition of imine (*R*)-**4b** to methyl acrylate benefits from HP assistance. The expected Michael adduct (*S*)-**5** was actually obtained with the same yield (80–85%), the same degree of regio- (>95%) and of stereoselectivity (93%) at 20°C, in 8 days at atmospheric pressure or in only 5 h under 1.4 GPa (Scheme 2).[13,14] Moreover, in the case of the related chiral β-enaminoesters, which generally require the use of Lewis acids to react with electrophilic alkenes, the application of the sole HP activation allows the formation of the Michael adducts, in the same range of regio- and stereoselectivity.[15]

The reactivity of methyl crotonate was investigated first.[14] Condensation of known imine (*R*)-**4a** [prepared from 2-methylcyclopentanone and (*R*)-1-phenylethylamine] with methyl crotonate (1 equiv., THF, 1.2 GPa, 20 h at 20°C) gave adduct (3*S*,1′*S*,1″*R*)-**6a**, *which turned out to be nearly homogeneous by* ^1H *and* ^{13}C *NMR spectroscopy*.[16] Hydrolysis of crude **6a** (20% aqueous AcOH, THF, 4 h at 20°C) next afforded ketoester (3*S*,1′*S*)-**7a**[17] with a 70% yield. The de and ee in **7a** were respectively ≥98 and 96%, determined by ^1H NMR spectroscopy, having added Eu(fod) and $Eu(hfc)_3$ as shift reagents (Scheme 3). By way of comparison, condensation of imine (*R*)-**4a** with methyl crotonate was investigated at atmospheric pressure. Under forced conditions (THF, 4 times addition of methyl crotonate of 2 equiv. each, 30 days at 67°C), a 9/1 mixture of quaternary/tertiary regioisomers was obtained after hydrolytic workup,



Scheme 2.

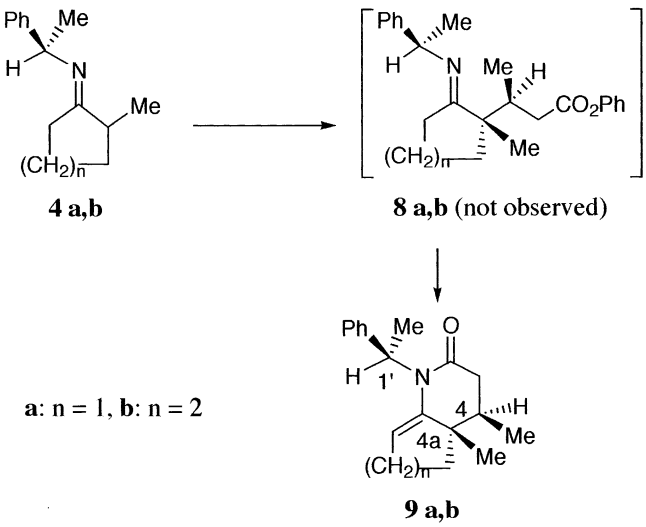


Scheme 3. *Reagents and conditions*: (a) 1 equiv. methyl crotonate, THF, 1.2 GPa, 20 h, 20°C; (b) 20% aqueous AcOH.

from which adduct (3*S*,1′*S*,1″*R*)-**6a** was isolated by flash chromatography on silica gel with a 34% yield, a 72% de and a 90% ee.

Condensation of known imine **4b** [derived from 2-methylcyclohexanone and (*R*)-1-phenylethylamine] with methyl crotonate (1 equiv., THF, 1.2 GPa, 20 h at 20°C) paralleled completely the conversion (**4a**→**7a**): ketoester (3*S*,1′*S*)-**7b**[18] was obtained with a 78% yield, a de ≥98%, and an ee of 94% (Scheme 3). Based on mechanistic considerations, the stereochemical course of these conjugate additions was vouchsafed by means of the X-ray diffraction analysis of lactam derivative **9b** (vide infra).

The reactivity of imines **4a**,**b** towards phenyl crotonate was investigated next. However, these condensations afforded invariably enantiopure bicyclic lactams (4*R*,4a*S*,1′*R*)-**9a**[19] and (4*R*,4a*S*,1′*R*)-**9b**[20] under HP (1 equiv. phenyl crotonate, THF, 0.7 GPa, 20°C, 22 h, 80% yield) or thermal conditions (1.6 equiv. phenyl crotonate, 120°C, 5 days, 55–60% yield) (Scheme 4). The formation



Scheme 4. *Reagents and conditions*: 1 equiv. phenyl crotonate, THF, 0.7 GPa, 22 h, 20°C or 1.6 equiv. phenyl crotonate, neat, 1 atm, 120 h, 120°C.

of lactams **9a**,**b** clearly involves a *N*-heterocyclization of the transient Michael adducts **8a**,**b**, a side reaction which reflects the marked nucleofugal ability of the phenoxy group.

The *syn* relationship between the two vicinal methyl groups at C-4 and C-4a in lactam **9a** was determined by ^{1}H NMR spectroscopy. The equatorial orientation of the C-4 methyl, *syn* to the C-4a axial angular methyl, was first revealed by inspection of the coupling constants between axial H-4 and the two adjacent protons at C-3 ($J_{H4ax-H3ax}=12.8$ Hz, $J_{H4ax-H3eq}=5.7$ Hz). This stereochemical assignment was further reinforced by NOESY experiments. However, because of the overlapping of the vicinal methyls signals in the NOESY chart, direct through-space interaction between these two groups was not analyzed. Finally, the *syn* arrangement of methyls was proved, exploiting a quartet of correlations: H-4 with α-H7 and equatorial α-H3, and C-4a methyl protons with β-H7 and axial β-H3 (Fig. 1).

On the other hand, the *syn* relationship between the two methyl groups, as well as the absolute configuration of the two newly created C-4 and C-4a stereocenters in homolog **9b**, were unequivocally assigned by X-ray diffraction analysis (Fig. 2).[21]

The remarkable stereochemical outcome observed in these conjugate additions can be interpreted by evoking that the reaction proceeds through the pseudo cyclic 'aza-ene-synthesis-like' transition state **10**, which involves as nucleophilic partners the more substituted secondary enamines, in tautomeric equilibrium with the starting imines **4a**,**b**.[22] In accordance with this mechanism, the proton borne by the nitrogen atom of enamines is transferred to the α-carbon atom of the crotonate partners, *concertedly* with the creation of the C–C bond. This requires a *synclinal* approach of the reactants, as shown in the Newman projection **11**.

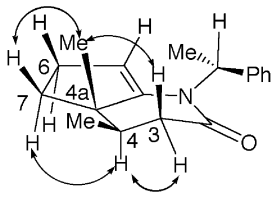


Figure 1. NOESY correlations in lactam **9a**.

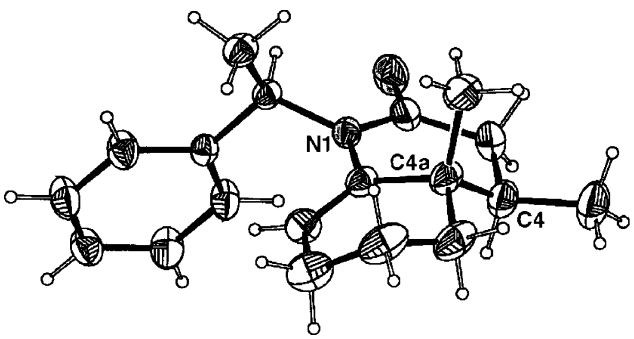
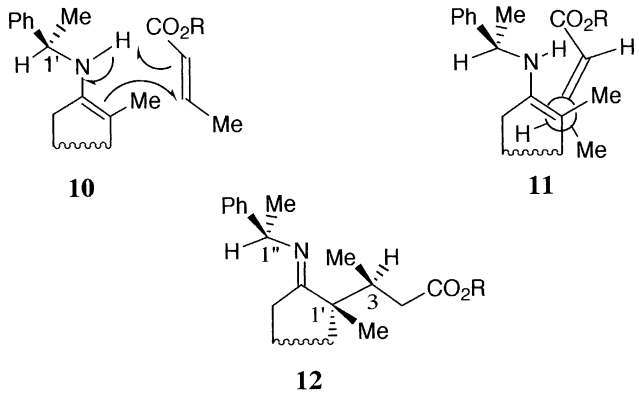


Figure 2. X-Ray crystal structure of lactam **9b**.



Scheme 5.

According to such a model, the alkylation takes place *anti* to the bulky phenyl group of the chiral amine moiety, portrayed in its energetically preferred conformation, minimizing the $A^{1,3}$-type strain (C1′–H bond more or less eclipsing the cyclopentene/cyclohexene ring). This accounts for the absolute configuration at C-1′ in adducts **12**. On the other hand, to rationalize the stereochemical relationship of the two newly created stereogenic carbon centers of these adducts, crotonates need to be arranged as depicted in approach **11**, namely with the ester group oriented '*endo*' relative to the enamine part of the nucleophilic partners (Scheme 5).

To conclude, we have set up a reliable method for achieving our original objective, namely the construction of a sterically congested pattern consisting of a QCC adjacent to a tertiary carbon center, frequently encountered in natural products. Since highly regio-, diastereo- and enantioselective, the HP-activated addition of chiral imines to alkyl/aryl crotonates reported in this paper indeed offers a direct, efficient solution to this complex synthetic problem.

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2. However, in the case of easily reversible processes this energy barrier is substantially lowered, making change in configuration feasible. A recent example is the racemization process at a QCC, involving a transient retro-Michael fragmentation, which affects certain Michael adducts (see Ref. 3g).
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16. Imine **6a**: pale yellow oil; IR (neat, cm^{-1}): ν 1738, 1673, 1603; ^1H NMR ($CDCl_3$, 200 MHz) δ: 7.13–7.40 (m, 5H), 4.45 (q, $J=6.5$ Hz, 1H), 3.96 (s, 3H), 2.95 (dd, $J=14.5$, 3.0 Hz, 1H), 2.05–2.48 (m, 4H), 2.02 (dd, $J=14.5$, 10.8 Hz, 1H), 1.30–1.92 (m, 3H), 1.41 (d, $J=6.5$ Hz, 3H), 1.04 (s, 3H), 0.91 (d, $J=6.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 180.4 (C), 174.1 (C), 146.0 (C), 127.9 (2 CH), 126.1 (2 CH) 125.4 (CH), 60.9 (CH), 51.0 (CH_3), 48.5 (C), 36.5 (CH_2), 35.2 (CH), 33.7 (CH_2), 28.7 (CH_2), 24.5 (CH_3), 21.5 (CH_3), 20.3 (CH_2), 15.0 (CH_3).
17. Ketone **7a**: colorless oil; $[\alpha]_D^{20}$ −30.9 (*c* 2.7, $EtOH_{abs}$); IR (neat, cm^{-1}): ν 1738; ^1H NMR ($CDCl_3$, 200 MHz) δ: 3.68 (s, 3H), 2.67 (dd, $J=15.1$, 3.7 Hz, 1H), 2.25–2.38 (m, 2H), 2.18 (m, 1H), 2.01 (dd, $J=15.1$, 10.3 Hz, 1H), 1.90–1.98 (m, 2H), 1.83 (m, 1H), 1.65 (m, 1H), 0.99 (s, 3H) 0.88 (dd, $J=6.7$, 0.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 221.9 (C), 173.0 (C), 50.9 (CH_3), 50.3 (CH), 37.9 (CH_2), 36.0 (CH_2), 33.9 (CH), 32.5 (CH_2), 19.0 (CH_3), 18.0 (CH_2), 14.9 (CH_3).
18. Ketone **7b**: colorless oil; $[\alpha]_D^{20}$ −91.2 (*c* 1.25, $EtOH_{abs}$). Lit.[7] (*ent*-**7b**): $[\alpha]_D^{20}$ +96 (*c* 3, EtOH).
19. Lactam **9a**: white solid, mp 64–65°C; $[\alpha]_D^{20}$+11.8 (*c* 3.4, $EtOH_{abs}$); IR (neat, cm^{-1}): ν 1665, 1629; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.30–7.70 (m, 5H), 6.20 (q, $J=7.1$ Hz, 1H), 4.40 (t, $J=2.0$ Hz 1H), 2.63 (dd, $J=18.3$, 5.7 Hz, 1H), 2.32 (dd, $J=18.3$, 12.8 Hz, 1H), 2.30 (m, 1H), 2.10 (ddd, $J=15.6$, 9.0, 3.1 Hz, 1H), 1.92 (ddq, $J=12.8$, 6.7, 5.7 Hz, 1H), 1.74 (dd, $J=12.2$, 7.3 Hz, 1H), 1.61 (d, $J=7.1$ Hz, 3H), 1.52 (m, 1H), 0.95 (s, 3H), 0.90 (d, $J=6.7$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 169.1 (C), 144.4 (C), 141.0 (C), 128.0 (2 CH), 126.3 (CH) 125.9 (2 CH), 105.0 (CH), 49.6 (CH), 46.8 (C), 37.7 (CH_2), 36.5 (CH_2), 36.5 (CH), 28.0 (CH_2), 14.8 (CH_3), 14.6 (CH_3), 14.4 (CH_3). Anal. calcd for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20. Found: C, 80.04; H, 8.56; N, 5.05.
20. Lactam **9b**: white solid; mp 70–71°C (pentane); $[\alpha]_D^{20}$ −77.3 (*c* 2.2, $EtOH_{abs}$); IR (neat, cm^{-1}): ν 1665, 1640; ^1H NMR ($CDCl_3$, 250 MHz) δ: 7.15–7.35 (m, 5H), 6.28 (q, $J=7.1$ Hz, 1H), 4.84 (dd, $J=5.6$, 2.7 Hz 1H), 2.66 (dd, $J=18.5$, 6.4 Hz, 1H), 2.26 (dd, $J=18.5$, 12.3 Hz, 1H), 1.72–2.10 (m, 5H), 1.59 (d, $J=7.1$ Hz, 3H), 1.40–1.55 (m, 1H), 1.30 (ddd, $J=12.5$, 3.0, 2.8 Hz, 1H), 0.98 (s, 3H), 0.91 (d, $J=6.7$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 168.9 (C), 142.3 (C), 140.5 (C), 128.2 (2 CH), 126.1 (CH) 125.4 (2 CH), 110.1 (CH), 50.4 (CH), 42.0 (C), 37.8 (CH_2), 36.4 (CH), 36.2 (CH_2), 24.9 (CH_2), 18.0 (CH_2), 15.8 (CH_3), 15.2 (CH_3), 14.3 (CH_3); MS *m*/*z* (EI, 70 eV): 283 (M^+, 13), 255 (3), 213 (6), 198 (4), 179 (76), 171 (14), 169 (48), 164 (53) 151 (14) 136 (17) 110 (35) 105 (100).
21. Crystal data for lactam **9b**: colorless crystal of 0.18×0.32×0.44 mm, $C_{19}H_{25}NO$, $M_w=283.40$; orthorhombic, space group $P2_12_12$, $Z=4$, $a=10.878$ (5), $b=17.438$ (7), $c=8.809$ (4) Å, $\beta=94.00$ (2)°, $V=1671$ Å^3, $d_c=1.127$ g cm^{-3}, $F(000)=616$, $\lambda=0.71073$ Å (Mo Kα), $\mu=0.07$ mm^{-1}; 18 750 reflections measured ($-14\leq h\leq 14$, $-25\leq k\leq 25$, $-13\leq l\leq 13$) on a Nonius Kappa CCD area-detector diffractometer. The structure was solved with SHELXL-86[23] and refined with SHELXL-93.[24] Hydrogen atoms riding. Refinement converged to $R(F)=0.0556$ for the 4276 observed reflections having $I\geq 2\sigma(I)$, and $wR_2=0.1381$ for all the 5560 unique data, goodness-of-fit $S=1.055$. Residual electron density: −0.14 and 0.17 e Å^{-3}. Full crystallographic results have been deposited as Supplementary Material (CIF file) at the Cambridge Crystallographic Data Centre, UK (CCDC 147894).
22. For an overview of this mechanism, see: Tran Huu Dau, M.-E.; Riche, C.; Dumas, F.; d'Angelo, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1059–1064 and references cited therein.
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