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Regiochemistry of the Condensation of 2-Aroyl-cyclohexanones and 2-Cyanoacetamide: ^{13}C-Labeling Studies and Semiempirical MO Calculations

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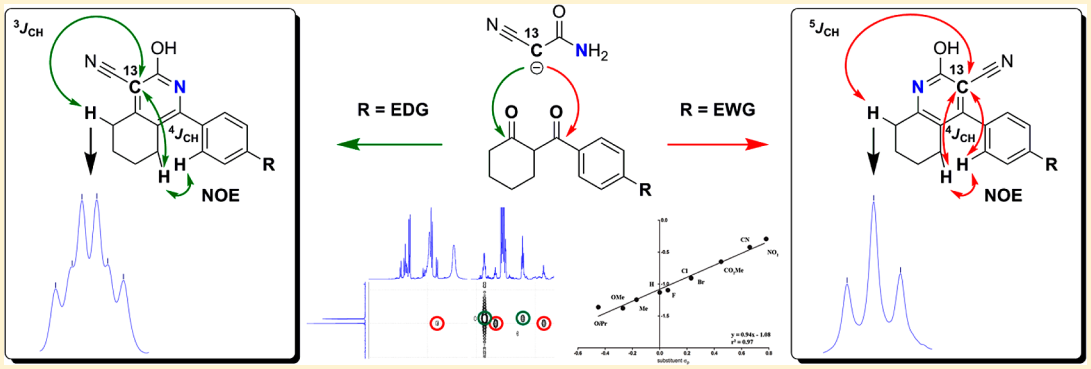
Supporting Information



ABSTRACT: Hydroxy-aryl-5,6,7,8-tetrahydroisoquinoline-4-carbonitriles represent interesting chemical scaffolds, but synthetic access to these compounds is limited. The reaction of 2-aroyl-cyclohexanones with 2-cyanoacetamide and base in ethanol has been reported to lead to the formation of the tetrahydroisoquinoline isomer. We show that depending on the electronic nature of the *para*-substituent on the aryl ring, formation of the regioisomeric tetrahydroquinoline isomer can significantly compete. The electron-donating or -withdrawing properties of the *para*-substituent of the aryl ring determines the ratio of product isomers. A series of 2-aroyl-cyclohexanones, with *para*-substituents ranging from electron-donating to electron-withdrawing, were reacted with [2-^{13}C]-cyanoacetamide. The product ratio and absolute regiochemistry were directly determined by quantitative ^{13}C, HMBC, and NOESY NMR spectroscopy on the reaction mixtures. A clear relationship between the regioisomeric product ratio and the Hammett sigma values of the substituents is demonstrated. This is explained by the separate in situ yields, which reveal that the pathway leading to the tetrahydroquinoline regioisomer is significantly more sensitive toward the electronic nature of the *para*-substituent than the pathway leading to the tetrahydroisoquinoline. Semiempirical AM1 molecular orbital calculations on the starting electrophile 2-aroyl-cyclohexanone support a correlation between the energy of the LUMOs and the regioisomeric product ratio. Our results facilitate synthetic access to a range of these interesting synthetic intermediates.

INTRODUCTION

The pharmaceutically interesting scaffold 6,7,8,9-tetrahydro-3*H*-pyrazolo[3,4-*c*]isoquinolin-1-amine **1** (Figure 1) has been identified as an important moiety in, for example, the development of kinase and phosphodiesterase inhibitors.[1−5] We previously reported this attractive fragment in our search for small-molecule inhibitors for the EPHA4 receptor tyrosine kinase.[6] For the synthesis of subsequently designed 5-aryl-6,7,8,9-tetrahydro-3*H*-pyrazolo[3,4-*c*]isoquinolin-1-amines (**2**), we explored 3-hydroxy-1-aryl-5,6,7,8-tetrahydroisoquinolines **3** as important intermediates.

Typically, such tetrahydroisoquinolines can be prepared via a condensation reaction between 2-cyanoacetamide and substituted cyclohexanones. Indeed, the reaction of 2-cyanoacetamide (**4**) with substituted 2-carbonyl-cyclohexanones (**5**) and different bases has been reported to yield the tetrahydroisoquinoline isomer **6** as the exclusive isolated product (Scheme 1).[7,8] However, it has been shown that for nonaroyl substituted **5**, the regioisomeric tetrahydroquinoline **7** is also formed, albeit to a smaller extent.[9] For example, the reaction of acetyl-substituted cyclohexanones with 2-cyanoacetamide has been reported to give rise to regioisomers depending on the conditions.[9] It can therefore be reasoned that the corresponding 2-aroyl-cyclohexanones may give regioisomers as well, giving either aryl-derivatized tetrahydroisoquinolines **3** or regioisomeric tetrahydroquinolines **8** (Figure 1) as products. In our previous work on kinase inhibitors,[6] we prepared a series

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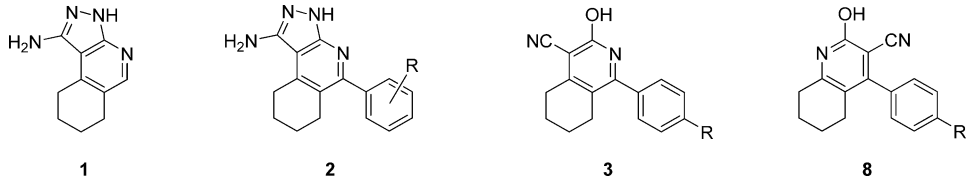
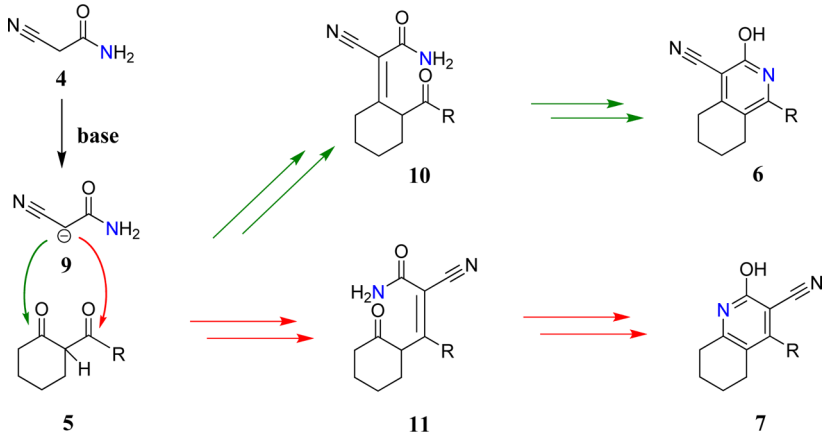
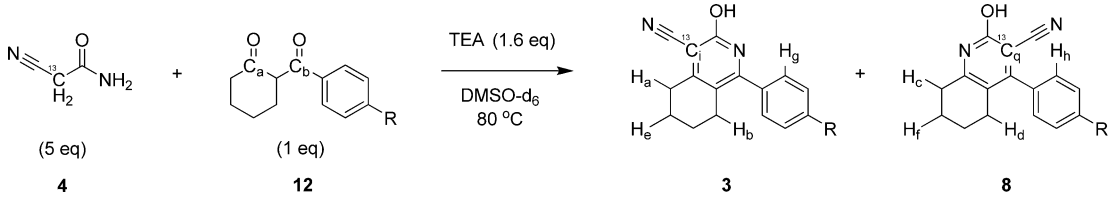


Figure 1. Chemical structures of scaffold **1**, EPHA4 kinase inhibitors **2**, and intermediates **3** and **8**.

Scheme 1. Proposed Reaction Pathways for the Formation of Regioisomers 6 and 7 from 2-Cyanoacetamide (4) and Substituted 2-Carbonyl-cyclohexanone (5)



Scheme 2. Reaction of [2-^{13}C]-Cyanoacetamide (4) with Substituted 2-Aroyl-cyclohexanones (12)[a]



[a]Carbon and hydrogen atoms that are important for correct spectroscopic identification and quantification of products **3** and **8** are labeled.

of tetrahydroisoquinolines **3**. The regiochemical identity of the products was validated by advanced 2D-NMR techniques. At the time we already noted that, depending on the nature of the substituent on the phenyl ring, both **3** and **8** were present in the crude reaction mixture. No molecular determinants underlying the regiochemistry of such condensations of 2-aroyl-cyclohexanones have been described so far in literature. We deemed an in-depth description of such determinants of value to define the synthetic scope and accessibility of these interesting heteroaromatic motifs **3** and **8**. Toward this end, we investigated the effect of a strategically chosen set of *para*-substituents on the in situ formations of tetrahydroisoquinoline (**3**) and tetrahydroquinoline (**8**) products, both experimentally (^{13}C-labeling) as well as theoretically (AM1 calculations).

RESULTS AND DISCUSSION

Design of a ^{13}C-Incorporation Approach. In the proposed reaction mechanism, **4** is deprotonated to stabilized enolate **9**, which attacks either carbonyl carbon atom of 2-carbonyl-cyclohexanone **5**, giving the respective regioisomeric Knoevenagel condensation intermediates **10** or **11** (Scheme 1). Upon subsequent ring closure via the amide nitrogen, followed by the elimination of water, the tetrahydroisoquinoline **6** or tetrahydroquinoline **7** product is formed. This description implies that the ultimate regiochemistry is determined by the initial site of attack on electrophile **5** by enolate **9**. It was hypothesized that, for 2-aroyl-cyclohexanone **12** as the electrophile (Scheme 2), the electronic nature of the *para*-aryl-substituent R could play a major role in the outcome of this reaction. That is, with R being an electron donating group (EDG), the electron density on carbon atom C_b is likely to be higher than the electron density on carbon atom C_a. This would favor an attack of enolate **9** on the more electrophilic C_a over an attack on C_b, ultimately resulting in the formation of the regioisomer **3**. If R is an electron-withdrawing group (EWG), however, the electron density on C_b decreases, resulting in greater electrophilicity and hence probably in increased competition between attack by enolate **9** on C_b over C_a. This would ultimately lead to higher amounts of regioisomer **8**. To investigate the effect of the electronic properties of the R group on product formations, we intended to react a number of substituted 2-aroyl-cyclohexanones **12** (with R-groups varying from electron-donating to electron-withdrawing) with **4**. The cyclohexanones **12** were synthesized by reaction of aroyl-chlorides with the enolate of cyclohexanone, albeit in low yields as a result of the purifications needed to achieve the high quality required for our experiments.

Conventional methods that could be used to determine product ratios as a result of regiochemistry (e.g., LC analysis)

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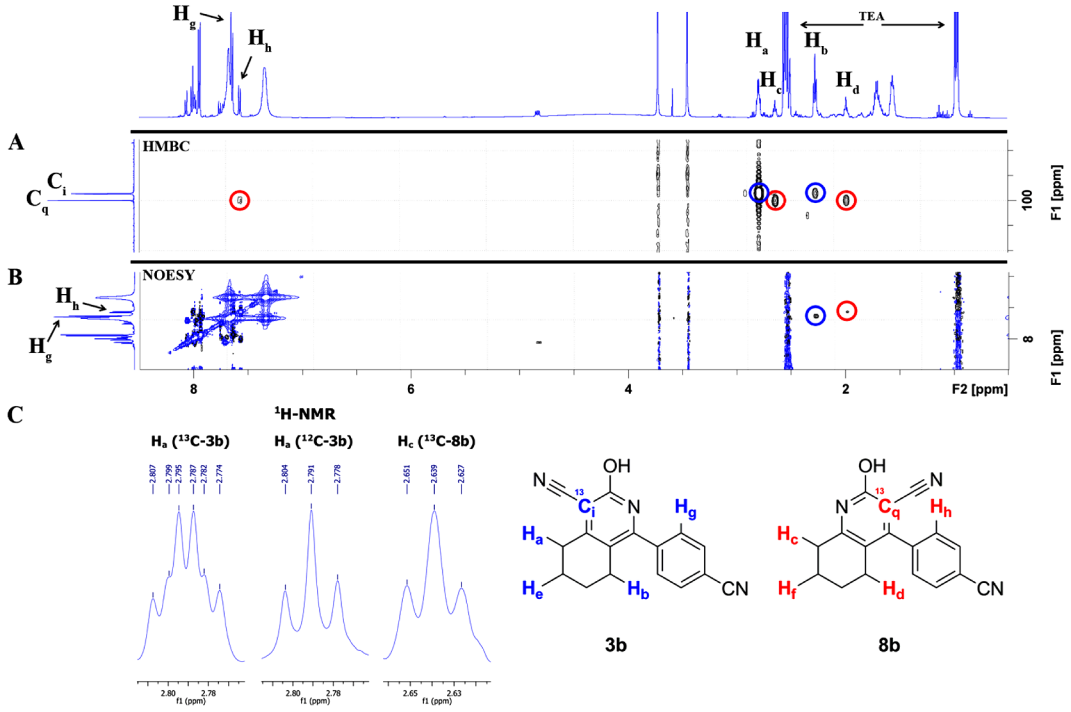

Figure 2. Representative analysis on the reaction mixture of **12b** (R = CN). (A) HMBC spectrum with observed couplings between C_i–H_a/H_b for isomer **3b** (blue circles) and C_q–H_h/H_c/H_d for isomer **8b** (red circles). (B) NOESY spectrum with observed couplings between H_g–H_b for isomer **3b** (blue circles) and H_h–H_d for isomer **8b** (red circles). (C) Magnification of ^{1}H NMR signals for H_a (in both ^{13}C-**3b** and separately ran ^{12}C-**3b**) and for H_c. Signals of H_g appear underneath the signals of one of the NH_2 hydrogen atoms of remaining **4**. The large doublet around 3.6 ppm is the CH_2 group from remaining **4** (split by ^{13}C).

have several drawbacks: (1) they require sample handling like dilution and/or filtration; (2) they cause exposure of any remaining starting materials or intermediates to eluents; and (3) in order to ensure accurate quantification of both isomers, by for example UV analysis, calibration curves for all regioisomers need to be produced. These procedures are quite elaborate and, more importantly, may cause deviation between the measured and true product ratios. Therefore, we strived to determine the product ratio directly, without any sample handling, from the crude reaction mixtures. A significant challenge associated with this approach is the requirement to determine absolute product regiochemistries from the reaction mixture. We envisioned that all requirements could be met in an approach using ^{13}C-labeling in combination with NMR spectroscopy. That is, aroyl-cyclohexanones **12** were reacted with excess ^{13}C-enriched 2-cyanoacetamide (hereafter referred to as **4**) and Et_3N base to form ^{13}C-enriched tetrahydroisoquinoline and ^{13}C-enriched tetrahydroquinoline products (hereafter referred to as **3** and **8**, respectively, Scheme 2). Given the only small difference in mass between ^{12}C- and ^{13}C-carbon atoms, we anticipate that any kinetic isotope effects would not lead to a significant deviation compared to use of ^{12}C-**4**. Since the reactions were run in DMSO-d_6, we also ensured that none of the CH_2 protons of **4** exchanged for deuterium atoms through base-assisted transfer from DMSO-d_6 (not shown). Reactions were run for 6 days at 80 °C and quantitative ^{13}C, HMBC, and NOESY NMR spectroscopy with appropriately set parameters (such as sufficient relaxation time) were performed on the reaction mixtures to get the necessary information on assignment of regiochemistry, in situ yields and product ratio. The area under the peak for the signal of carbon atom C_q (**8**) and C_i (**3**) was standardized to mmol amounts by using an external standard of **4** in DMSO-d_6. Mass identities were established using LC–MS. Regiochemistry was assigned as illustrated in detail in the next paragraph.

Assignment of Regiochemistry. Figure 2 shows the HMBC and NOESY NMR spectra of a representative reaction mixture started with diketone **12b** (R = CN). Quantitative ^{13}C NMR analysis on the chemically different ^{13}C-enriched carbon atoms of the regioisomers (i.e., C_i and C_q) enables direct comparison of mmol amounts. The ^{13}C NMR signals of C_i and C_q are clearly visible as large peaks at ∼98 and ∼100 ppm and are typically separated by 1.0–1.5 ppm (Figure 2A; peak widths differ, see the Supporting Information). By means of HMBC NMR analysis, coupling between C_i and hydrogen atoms H_a/H_b is visible (Figure 2A). Coupling between C_i and aromatic H_g is not observed because of the distance of six bond lengths between these atoms. In contrast, for C_q a coupling is observed with H_c/H_d as well as with aromatic H_h. Typically, couplings over two to three and sometimes up to four bonds may be visible in HMBC NMR. Because of the ^{13}C-enrichment, however, we also observed couplings over five bond lengths. A NOESY NMR experiment pairs H_g with H_b and H_h with H_d (Figure 2B), confirming the correct association of atoms C_q to H_h and, hence, the correct assignment of C_q to tetrahydroquinoline **8**. More broadly, confirmatory proof for this assignment could be obtained from the ^{1}H NMR spectrum. Atom H_a couples with H_e but also with nearby C_i, resulting in a triplet of doublet for H_a ($^3J_{CH}$ ∼ 3.9 Hz) (Figure 2C). None of the other benzylic methylene groups (H_b, H_c, H_d) show this extra splitting, since they are further away from the ^{13}C center (exemplified for H_f-coupled H_c in Figure 2C). Moreover, this extra splitting for H_a is absent when the same incubation is performed with **12b** and ^{12}C-**4** (Figure 2C, labeled H_a(^{12}C-

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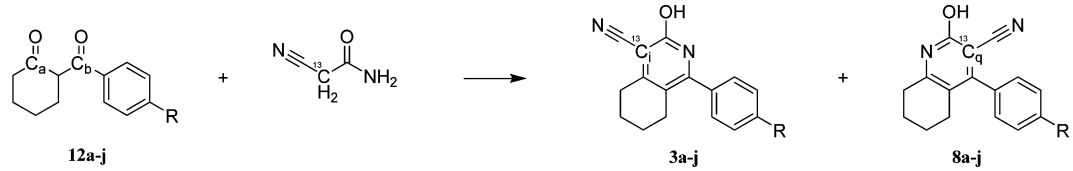
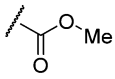
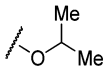
Table 1. (Left) Regioisomeric Ratios and in Situ Yields for Products 3 and 8 and (Right) MO Energy Calculations on Starting Materials 12



		Experimental data [a]					MO energy calculations on starting materials **12** [b]		
cmpd	R	σ_p	regioisomeric product ratio **8** : **3**	log regioisomeric product ratio **8** : **3**	in situ yield (%) **8**	in situ yield (%) **3**	LUMO energy (eV)	LUMO+ energy (eV)	Δ LUMO (eV)
a		0.78	0.51	-0.29	29	57	-1.712	0.478	2.190
b		0.67	0.38	-0.42	24	62	-1.202	0.511	1.713
c		0.45	0.22	-0.65	15	66	-1.166	0.534	1.700
d		0.23	0.12	-0.91	9	73	-0.787	0.451	1.238
e		0.23	0.12	-0.91	10	77	-0.718	0.484	1.202
f		0.06	0.080	-1.10	7	83	-0.444	0.597	1.041
g		0.00	0.074	-1.13	6	83	-0.721	0.472	1.193
h		-0.17	0.057	-1.24	5	82	-0.404	0.621	1.025
i		-0.27	0.042	-1.38	3	82	-0.393	0.640	1.033
j		-0.45	0.043	-1.36	3	59	-0.343	0.666	1.009

[a]Regioisomeric ratios and in situ yield by ^{13}C NMR spectroscopy were determined as outlined. [b]Semiempirical MO calculations were performed using AM1. σ_p = Hammett *para*-value.

3b)). This observation confirms the correct assignment of C_i to **3**. The protocols described here could be used consistently and with similar results for incubations on **12a–j**. It should be noted that with decreasing amounts (vide infra) of tetrahydroquinoline **8** being formed for compounds **12f–j**, the HMBC correlation of C_q to H_h became too weak to be clearly visible. Assuringly, though, in these cases all discussed key HMBC peaks to the benzylic groups (H_a, H_b, H_c and H_d) remained consistently visible, as did the additional splitting of H_a by C_i. Moreover, the chemical shifts of the benzylic groups (H_a, H_b, H_c, H_d) and of ^{13}C labels (C_i, C_q) were found not to change significantly in the incubations on series **12a–j**. All of this assures correct assignment of C_q to **8** in the cases where amounts of **8** were low. Last, analytical data for all major isomers **3** in the incubations were in accord with data of authentic pure ^{12}C-**3**, prepared by us previously[6] or synthesized new (see the Experimental Section). A representative member of the **8** class (i.e., ^{12}C-**8a**) was isolated for the same purpose, and its data also correspond to the analysis of **8a** in the corresponding incubation.

Effect of Varying R-Groups on Product Profiles. Given that our initial hypothesis was based on electronic effects of R most notably on C_b (Scheme 2), substituents were selected on the basis of the Hammett σ_p values[10] (Table 1, left). We used the σ_p values as assembled by Hansch et al.[11] Table 1 shows the product profiles per R-group. It is apparent that a correlation between the electronic properties of the *para*-substituent R and the log of the observed regioisomeric ratio exists (Figure 3A). Compared to R = H (**12g**), introduction of EWG ($\sigma_p > 0$) gives a significant increase in amount of isomer **8** compared to the amount of isomer **3**. For the strongest EWG (R = NO_2, **12a**), the regioisomeric ratio **8**:**3** is ∼1:2 (Table 1). Upon introduction of EDG ($\sigma_p < 0$), the regioisomeric ratio decreases slightly compared to R = H. Taking into account that two

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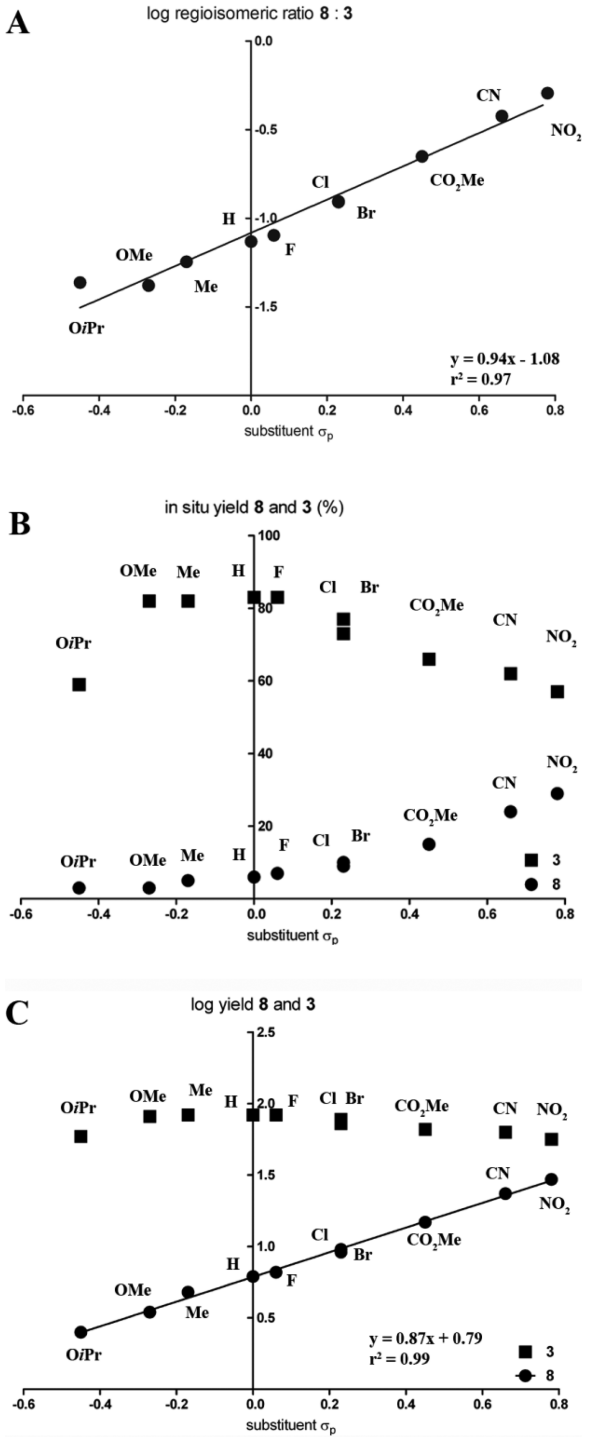

Figure 3. Correlation between the electronic properties of R and (A) log of observed regioisomeric ratio (**8**:**3**); (B) in situ yield (%) of **8** and **3**; and (C) log of in situ yield (%) of **8** and of **3**. σ_p = Hammett *para*-value.

mechanistic pathways are operative for the regioisomers (Scheme 1), we dissected the Hammett plot into plots for the (log of) in situ yield of each isomer (Figure 3B,C). Figure 3C reveals that formation of isoquinoline **3** is relatively insensitive to electronic substituent effects. In contrast, formation of quinoline **8** is favored by EWG substituents, as indicated by the positive slope of the trend line. The relatively lower total conversion with **12j** is noteworthy, but the expected extremely low amounts of **8** (and associated errors) with even increased EDG character did not permit us to investigate beyond this point.

MO Calculations. Considering the competing reaction mechanisms, we investigated whether FMO theory could substantiate our experimental results. Toward this end, we assume that the reaction occurs between enolate **9** and the dicarbonyl tautomeric form of electrophiles **12** and not on any enol form of **12**.[12] Given that C_a/C_b are the sites of attack determining regiochemistry (Scheme 2), we calculated energy levels of the **12a−j** lowest unoccupied molecular orbitals (LUMOs) in which C_a and C_b are significantly participating (Table 1 and Figure 4). A representative visualization of the LUMO of **12g** (Figure 4B) shows that C_b is involved in the LUMO, while C_a is not significantly. Therefore, we also addressed the energies of the LUMO in which C_a is involved (referred to as LUMO+, visualized for **12g** in Figure 4C) in compounds **12**.

If the reactions would be dominated by HOMO−LUMO effects, the HOMO of enolate **9** should preferably combine with the LUMO of compounds **12**. This would make C_b the inherently preferred site of attack by **9** and should result in a majority of tetrahydroquinoline **8**. From our experimental results, however, it is clear that the major product is always tetrahydroisoquinoline **3**, resulting from attack of **9** on carbon C_a. LUMO+ (involving C_a) remains virtually constant in energy in all starting materials **12** (Table 1 and Figure 4A). Thus, although the energy level of the LUMO is consistently lower than that of the LUMO+ in all diketones **12a−j**, we hypothesize that activation strain (i.e., reagent deformation)[13−15] associated with the transition state may be intrinsically higher for attack on C_b, arguably for steric and/or conjugation effects. This may cause attack on C_a (i.e., combination with LUMO+) to dominate over attack on C_b. Upon introduction of stronger EWG substituents, however, the energy of the LUMO decreases to such an appreciable level (Table 1 and Figure 4A) that carbon atom C_b gets increasingly attacked by enolate **9**. In all, the energy difference between LUMO+ and LUMO (ΔLUMO) correlates reasonably well in a positive fashion with the regioisomeric ratio (Figure 4A).

The results of the ^{13}C-labeling experiments as well as AM1 calculations may be reconciled in one overall explanation. Key is that two competing mechanisms can in principle operate: initial attack on carbon atom C_a to give tetrahydroisoquinolines or on C_b to give tetrahydroquinolines (shown in Scheme 2). Our experimental data show that these two mechanisms have different sensitivities toward the electronic properties of R: the pathway through C_a is relatively insensitive, while the pathway through C_b is significantly favored by EWG groups. This is supported by our calculations, which show little variation of LUMO+ energy levels but substantial lowering of LUMO energy levels (in which C_b is involved) by introduction of EWG groups. Practically, this means that with electron-donating substituents, attack is almost exclusively at C_a giving tetrahydroisoquinolines. As the EWG-capacity of R increases, attack on C_b and thus tetrahydroquinoline formation increasingly competes.

■ CONCLUSION

In this work, we describe factors that govern the regioisomeric outcome of the reaction of substituted 2-aroyl-cyclohexanones with 2-cyanoacetamide. By incorporating a ^{13}C-enriched carbon atom into the two products (tetrahydroisoquinolines **3** and

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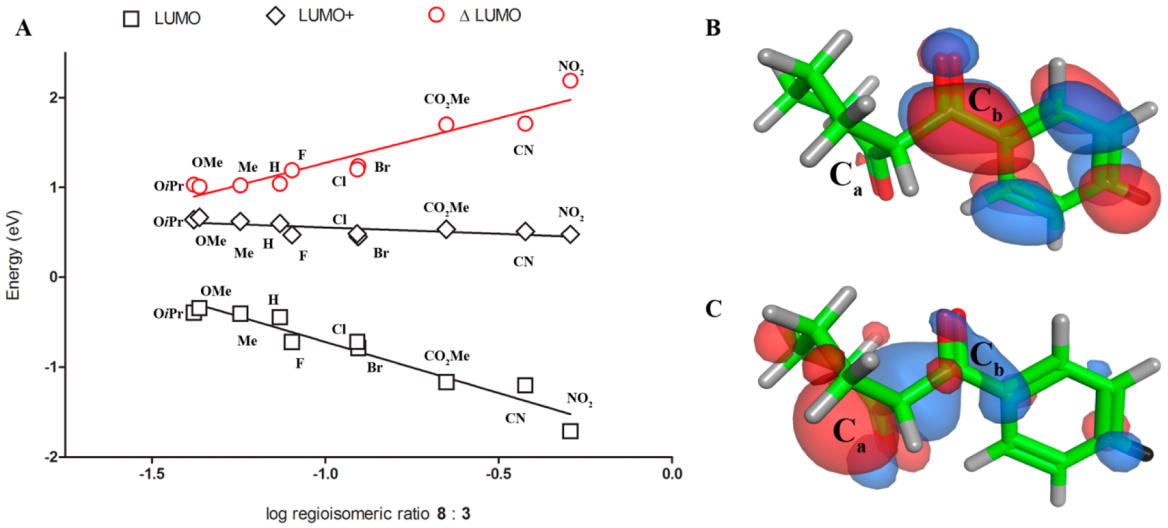

Figure 4. (A) Correlation between the log of the observed regioisomeric ratio **8**:**3** and the calculated energy (eV) of the LUMO and LUMO+ in starting materials **12**. The difference in LUMO+ and LUMO energy (Δ LUMO) is indicated by red circles in the graph. (B) Representative visualization of the LUMO in **12g** (R = H). (C) Representative visualization of the LUMO in which C_a is involved (LUMO+) in **12g** (R = H).

regioisomeric tetrahydroquinolines **8**) we were able to distinguish between both regioisomers in the reaction mixture using HMBC and NOESY NMR spectroscopy. The in situ product profile was determined using quantitative ^{13}C NMR spectroscopy. A correlation between the electronic properties of the *para*-substituent and the regioisomeric product ratio is demonstrated, which results from the distinctly differing electronic sensitivities of the two involved competing pathways. Semiempirical MO calculations on the starting materials **12** support the notion that a combination of activation strain and of the energy gap between the LUMO and LUMO+ is responsible for the observed regioisomeric ratios. From a practical point of view, our work provides useful entries to this interesting class of heterocycles and provides some guidelines for synthetic planning en route to both regioisomeric forms. For example, our results show that use of a nitro-substituent followed by a reduction provides a route to the synthesis of an otherwise difficult-to-synthesize amine-substituted tetrahydroquinoline isomer.

EXPERIMENTAL SECTION

General Experimental Procedures. Chemicals and reagents were obtained from commercial suppliers and were used without further purification. ^1H and ^{13}C NMR chemical shifts (δ) were internally referenced to the residual solvent peak. LC−MS analyses were performed using the following conditions: Xbridge (C18) 5 μm column (100 × 4.6 mm) with solvent A (water with 0.1% formic acid) and solvent B (acetonitrile with 0.1% formic acid), flow rate of 1.0 mL/min, start 5% B, linear gradient to 90% B in 5 min, then 5 min at 90% B, then 5 min at 5% A, total run time of 15 min. HRMS detection was performed with an ESI hybrid quadrupole time of flight mass spectrometer, except for compound **12b**, which was analyzed with an ion trap time of flight mass spectrometer.

[2-^{13}C]-Cyanoacetic acid.[16] [2-^{13}C]-Bromoacetic acid (1.34 g, 9.6 mmol) was dissolved in water (30 mL). In small portions, potassium carbonate (1.33 g, 9.6 mmol) was added. Potassium cyanide (625 mg, 9.6 mmol) was added, and the mixture was heated at reflux temperature for three hours and stirred overnight at room temperature. The flask was cooled in an ice bath, and concentrated aq HCl (2 mL) was added to the mixture dropwise (***Caution!*** *Potential release of HCN gas!*). At room temperature, solid sodium chloride was added to the mixture until the solution was saturated. The resulting solution was extracted with EtOAc (6 × 50 mL). The combined organic phases were dried over Na_2SO_4 and evaporated in vacuo to yield 744 mg (8.6 mmol, 90%) of the title compound as a colorless solid material: ^1H NMR (500 MHz, DMSO-d_6) δ (ppm) 13.32 (br s, 1H, OH), 3.86 (d, $^1J_{CH}$ = 136.5 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 165.8 (d, $^1J_{CC}$ = 57.6 Hz, C═O), 115.6 (d, $^1J_{CC}$= 60.5 Hz, CN), 24.7 (CH_2, ^{13}C-labeled, intense peak).

[2-^{13}C]-Cyanoacetamide (4). [2-^{13}C]-Cyanoacetic acid (700 mg, 8.13 mmol) was dissolved in dry DCM (25 mL). In small portions, oxalyl chloride (2.0 M in DCM, 4.5 mL, 9.0 mmol) was added to the mixture followed by two drops of DMF. The reaction mixture was heated at reflux temperature for 3 h, during which it colored yellow. After cooling to room temperature, NH_3 gas was bubbled through the mixture for 10 min, and the formed suspension was stirred at room temperature for 30 min. The solvent was evaporated in vacuo, and the yellow colored solid material was suspended in distilled THF, followed by filtration and subsequent washing of the residue with THF. The wash fractions were combined, and the solvent was evaporated in vacuo to yield 667 mg of the crude product as a yellow colored solid material. The product was recrystallized from EtOH (95%) in several batches to yield 400 mg (4.7 mmol, 58%) of the title compound as a light-yellow colored solid material: ^1H NMR (500 MHz, DMSO-d_6) δ (ppm) 7.64 (s, 1H), 7.34 (s, 1H), 3.58 (d, $^1J_{CH}$ = 135.5 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm) 164.1 (d, $^1J_{CC}$ = 47.9 Hz, CN), 116.3 (d, $^1J_{CC}$ = 60.1 Hz, C═O), 25.3 (CH_2, ^{13}C-labeled, intense peak).

General Method A. The following method is representative for the synthesis of substituted 2-aroyl-cyclohexanones **12a**−**j**. ^1H and ^{13}C NMR experiments on the products were conducted in $CDCl_3$. Under those conditions, all products were >95% in the keto form (labeled KETO) or enol form (labeled ENOL, **12b** only) as judged from ^1H NMR spectra.

2-(4-Nitrobenzoyl)cyclohexanone (12a). Under nitrogen atmosphere, 7.5 mL of LDA (2.0 M in THF, 15 mmol) was added to dry THF (25 mL) at −78 °C. Cyclohexanone (1.47 g, 15 mmol) dissolved in 5 mL of dry THF was added dropwise to the mixture. After stirring the solution for 45 min at −78 °C, 4-nitrobenzoyl chloride (2.78 g, 15 mmol) dissolved in 5 mL of dry THF was added dropwise. The mixture was allowed to warm up and stirred for 2 h at room temperature. The mixture was quenched with 15 mL of HCl (2M). Water (20 mL) was added, and the product was extracted with diethyl ether (2 × 20 mL). The combined organic layers were washed with 1.0 M aq $NaHCO_3$, dried over Na_2SO_4 and concentrated in vacuo to yield a brown colored oil. Purification by flash chromatography (75% petroleum ether/23% $CHCl_3$/2% TEA) and subsequent recrystallization from petroleum ether (60−80) yielded 150 mg (0.61 mmol, 4%)

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of the title compound as white crystals: ^{1}H NMR KETO (500 MHz, $CDCl_3$) δ (ppm) 8.29 (d, J = 8.8 Hz, 2H), 8.02 (d, J = 8.8 Hz, 2H), 4.36 (dd, J = 9.5, 5.7 Hz, 1H), 2.53 (t, J = 6.1 Hz, 2H), 2.35−2.24 (m, 1H), 2.23−2.12 (m, 1H), 2.12−1.99 (m, 2H), 1.96−1.83 (m, 1H), 1.83−1.71 (m, 1H); ^{13}C NMR KETO (126 MHz, $CDCl_3$) δ 208.2, 196.5, 150.4, 141.3, 129.6, 124.0, 59.5, 42.6, 29.7, 27.4, 23.5; LC−MS (ESI) m/z calcd for $C_{13}H_{14}NO_4$ 248.09 $[M + H]^+$, found 248.1.

4-(2-Oxocyclohexanecarbonyl)benzonitrile (12b). Synthesized from 4-cyanobenzoyl chloride (2.5 g, 15 mmol) according to General Method A. Yield 340 mg (1.5 mmol, 10%) of the title compound as white crystals: mp 101.3−103.5 °C; ^{1}H NMR ENOL (500 MHz, $CDCl_3$) δ (ppm) 16.47 (s, 1H), 7.72 (d, J = 8.1 Hz, 2H), 7.62 (d, J = 8.2 Hz, 2H), 2.50 (t, J = 6.7 Hz, 2H), 2.33 (t, J = 6.1 Hz, 2H), 1.82−1.73 (m, 2H), 1.67−1.59 (m, 2H); ^{13}C NMR ENOL (126 MHz, $CDCl_3$) δ 191.1, 188.7, 141.6, 132.2, 128.3, 118.3, 114.0, 107.3, 32.9, 26.3, 23.4, 21.8; HRMS (EIMS) m/z calcd for $C_{14}H_{12}NO_2$ 226.0874 $[M - H]^-$, found 226.0886.

Methyl 4-(2-oxocyclohexanecarbonyl)benzoate (12c). Synthesized from methyl 4-(chlorocarbonyl)benzoate (2.0 g, 10 mmol) according to General Method A. Yield 190 mg (0.73 mmol, 7%) of the title compound as white crystals: ^{1}H NMR KETO (500 MHz, $CDCl_3$) δ (ppm) 8.10 (d, J = 8.4 Hz, 2H), 7.92 (d, J = 8.4 Hz, 2H), 4.37 (dd, J = 8.8, 5.8 Hz, 1H), 3.94 (s, 3H), 2.60−2.45 (m, 2H), 2.38−2.24 (m, 1H), 2.19−2.09 (m, 1H), 2.07−1.96 (m, 2H), 1.96−1.84 (m, 1H), 1.82−1.69 (m, 1H); ^{13}C NMR KETO (126 MHz, $CDCl_3$) δ 208.4, 197.4, 166.3, 139.9, 134.1, 130.0, 128.5, 59.2, 52.6, 42.5, 29.9, 27.4, 23.3; HRMS (EIMS) m/z calcd for $C_{15}H_{16}NaO_4$ 283.0946 $[M + Na]^+$, found 283.0941.

2-(4-Bromobenzoyl)cyclohexanone (12d). Synthesized from 4-bromobenzoyl chloride (3.28 g, 15 mmol) according to General Method A. Yield 610 mg (2.17 mmol, 15%) of the title compound as white crystals: ^{1}H NMR KETO (500 MHz, $CDCl_3$) δ (ppm) 7.75 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 8.6 Hz, 2H), 4.30 (dd, J = 8.4, 5.9 Hz, 1H), 2.59−2.42 (m, 2H), 2.34−2.23 (m, 1H), 2.16−2.06 (m, 1H), 2.06−1.84 (m, 3H), 1.80−1.68 (m, 1H); ^{13}C NMR KETO (126 MHz, $CDCl_3$) δ 208.5, 196.6, 135.4, 132.1, 130.1, 128.6, 58.9, 42.4, 29.9, 27.4, 23.3; HRMS (EIMS) m/z calcd for $C_{13}H_{13}BrNaO_2$ 302.9997 $[M + Na]^+$, found 302.9991.

2-(4-Chlorobenzoyl)cyclohexanone (12e). Synthesized from 4-chlorobenzoyl chloride (1.81 g, 10 mmol) according to General Method A. Yield 984 mg (3.01 mmol, 29%) of the title compound as white crystals: ^{1}H NMR KETO (500 MHz, $CDCl_3$) δ (ppm) 7.82 (d, J = 8.6 Hz, 2H), 7.42 (d, J = 8.6 Hz, 2H), 4.31 (dd, J = 8.4, 5.9 Hz, 1H), 2.59−2.44 (m, 2H), 2.35−2.22 (m, 1H), 2.16−2.07 (m, 1H), 2.07−1.84 (m, 3H), 1.82−1.67 (m, 1H); ^{13}C NMR KETO (126 MHz, $CDCl_3$) δ 208.5, 196.4, 139.9, 135.0, 130.1, 129.1, 59.0, 42.4, 30.0, 27.4, 23.3; HRMS (EIMS) m/z calcd for $C_{13}H_{13}ClNaO_2$ 259.0502 $[M + Na]^+$, found 259.0496.

2-(4-Fluorobenzoyl)cyclohexanone (12f). Synthesized from 4-fluorobenzoyl chloride (2.38 g, 15 mmol) according to General Method A. Yield 770 mg (3.5 mmol, 23%) of the title compound as white crystals: ^{1}H NMR KETO (500 MHz, $CDCl_3$) δ (ppm) 7.92 (dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{HF}$ = 5.4 Hz, 2H), 7.11 (t, J = 8.6 Hz, 2H), 4.33 (dd, J = 7.9, 6.1 Hz, 1H), 2.61−2.43 (m, 2H), 2.37−2.25 (m, 1H), 2.16−2.06 (m, 1H), 2.06−1.85 (m, 3H), 1.81−1.68 (m, 1H); ^{13}C NMR KETO (126 MHz, $CDCl_3$) δ 208.6, 196.0, 165.9 (d, $^1J_{CF}$ = 255.3 Hz), 133.2 (d, $^4J_{CF}$ = 3.0 Hz), 131.3 (d, $^3J_{CF}$ = 9.4 Hz), 115.9 (d, $^2J_{CF}$ = 21.9 Hz), 58.9, 42.4, 30.0, 27.4, 23.2; HRMS (EIMS) m/z calcd for $C_{13}H_{13}FNaO_2$ 243.0797 $[M + Na]^+$, found 243.0792.

2-Benzoylcyclohexanone (12g). Synthesized from benzoyl chloride (2.62 g, 15 mmol) according to General Method A. Yield 830 mg (4.1 mmol, 27%) of the title compound as white crystals: ^{1}H NMR KETO (500 MHz, $CDCl_3$) δ (ppm) 7.89 (d, J = 8.2 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.7 Hz, 2H), 4.37 (dd, J = 7.6, 6.4 Hz, 1H), 2.63−2.44 (m, 2H), 2.37−2.25 (m, 1H), 2.15−2.05 (m, 1H), 2.05−1.85 (m, 3H), 1.80−1.69 (m, 1H); ^{13}C NMR KETO (126 MHz, $CDCl_3$) δ 208.7, 197.7, 136.7, 133.4, 128.8, 128.6, 58.9, 42.4, 30.1, 27.4, 23.2; HRMS (EIMS) m/z calcd for $C_{13}H_{14}NaO_2$ 225.0891 $[M + Na]^+$, found 225.0886.

2-(4-Methylbenzoyl)cyclohexanone (12h). Synthesized from 4-methylbenzoyl chloride (2.81 g, 18 mmol) according to General Method A. Yield 1.04 g (4.8 mmol, 26%) of the title compound as white crystals: mp 98.9−103.7 °C; ^{1}H NMR KETO (500 MHz, $CDCl_3$) δ (ppm) 7.79 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 7.9 Hz, 2H), 4.35 (t, J = 7.0 Hz, 1H), 2.63−2.52 (m, 1H), 2.52−2.43 (m, 1H), 2.39 (s, 3H), 2.35−2.24 (m, 1H), 2.15−2.04 (m, 1H), 2.04−1.86 (m, 3H), 1.81−1.68 (m, 1H); ^{13}C NMR KETO (126 MHz, $CDCl_3$) δ 208.9, 197.2, 144.3, 134.2, 129.5, 128.8, 58.9, 42.4, 30.2, 27.4, 23.1, 21.8; HRMS (EIMS) m/z calcd for $C_{14}H_{16}NaO_2$ 239.1048 $[M + Na]^+$, found 239.1043.

2-(4-Methoxybenzoyl)cyclohexanone (12i). Synthesized from 4-methoxybenzoyl chloride (2.6 g, 15 mmol) according to General Method A. Yield 761 mg (3.3 mmol, 21%) of the title compound as white crystals: ^{1}H NMR KETO (500 MHz, $CDCl_3$) δ (ppm) 7.87 (d, J = 8.9 Hz, 2H), 6.90 (d, J = 8.9 Hz, 2H), 4.32 (t, J = 6.5 Hz, 1H), 3.84 (s, 3H), 2.61−2.50 (m, 1H), 2.50−2.40 (m, 1H), 2.34−2.24 (m, 1H), 2.11−1.86 (m, 4H), 1.78−1.66 (m, 1H); ^{13}C NMR KETO (126 MHz, $CDCl_3$) δ 208.9, 195.9, 163.7, 131.0, 129.7, 113.9, 58.6, 55.6, 42.3, 30.2, 27.4, 23.1; HRMS (EIMS) m/z calcd for $C_{14}H_{16}NaO_3$ 255.0997 $[M + Na]^+$, found 255.0992.

2-(4-Isopropoxybenzoyl)cyclohexanone (12j). Synthesized from 4-isopropoxybenzoyl chloride (2.08 g, 26.8 mmol) according to General Method A. Yield 683 mg (2.62 mmol, 25%) of the title compound as white crystals: mp 105.1−106.7 °C; ^{1}H NMR KETO (500 MHz, $CDCl_3$) δ 7.86 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 4.68−4.58 (m, 1H), 4.32 (t, J = 6.5 Hz, 1H), 2.61−2.53 (m, 1H), 2.51−2.42 (m, 1H), 2.37−2.26 (m, 1H), 2.11−1.97 (m, 2H), 1.97−1.89 (m, 2H), 1.78−1.67 (m, 1H), 1.35 (d, J = 6.1 Hz, 6H); ^{13}C NMR KETO (126 MHz, $CDCl_3$) δ 209.0, 195.8, 162.3, 131.1, 129.2, 115.3, 70.3, 58.7, 42.3, 30.3, 27.4, 23.1, 22.0; HRMS (EIMS) m/z calcd for $C_{16}H_{20}NaO_3$ 283.1310 $[M + Na]^+$, found 283.1305.

General Method B. The following method is representative for the reactions of 2-aroyl-cyclohexanones **12** with [2-^{13}C]-cyanoacetamide **4**.

Reaction of [2-^{13}C]-Cyanoacetamide (4) with 2-(4-Nitrobenzoyl)cyclohexanone (12a) to Yield 3a and 8a. In a sealable NMR tube, 2-(4-nitrobenzoyl)cyclohexanone (**12a**) (8.68 mg, 0.035 mmol) was dissolved in 442 μL of DMSO-d_6. Then, 50 μL of [2-^{13}C]-cyanoacetamide (**4**) stock solution (0.30 mg/μL of DMSO-d_6, 15 mg, 0.176 mmol) and triethylamine (8.0 μL, 0.057 mmol) were added (total volume 500 μL). The headspace above the mixture was shortly flushed with nitrogen gas, and the NMR tube was sealed with a screw cap. Samples were heated at 80 °C for 6 days. All samples remained clear during incubations. After that, samples were cooled to room temperature (all samples remained clear). NMR experiments were recorded on the reaction mixtures to assign absolute regiochemistries (^{1}H, HMBC, and NOESY NMR spectroscopy) and to determine the peak areas for C_i and C_q (quantitative ^{13}C NMR spectroscopy with a long D1 parameter of 80 s; spectra are available in the Supporting Information). Peak area standardization was done by DMSO-normalized comparison of peak areas to the peak area observed in a ^{13}C NMR spectrum (D1 = 80 s) of an external standard of [2-^{13}C]-cyanoacetamide **4** (15 mg) in DMSO-d_6 (500 μL). LC−MS experiments were conducted on the mixtures to confirm the masses of the ^{13}C-enriched products (two baseline separated peaks are observed for **3a** and **8a**, $[M + H]^+$ and retention time (min) are reported): ^{13}C NMR (only signals of ^{13}C-enriched C_i (**3a**) and C_q (**8a**) are reported) (126 MHz, $CDCl_3$) δ 99.86, 97.74; LC−MS (ESI) m/z calcd for $C_{15}{}^{13}CH_{14}N_3O_3$ 297.11 $[M + H]^+$, found 297.0 (4.89 min) and 297.0 (5.06 min); HRMS (EIMS) m/z calcd for $C_{15}{}^{13}CH_{14}N_3O_3$ 297.1063 $[M + H]^+$, found 297.1056.

Reaction of [2-^{13}C]-Cyanoacetamide (4) with 4-(2-Oxocyclohexanecarbonyl)benzonitrile (12b) to Yield 3b and 8b. Performed according to General Method B: ^{13}C NMR (only signals of ^{13}C enriched C_i (**3**) and C_q (**8**) are reported) (126 MHz, $CDCl_3$) δ 99.93, 98.28; LC−MS (ESI) m/z calcd for $C_{16}{}^{13}CH_{14}N_3O$ 277.12 $[M + H]^+$, found 277.0 (4.64 min) and 277.0 (4.89 min); HRMS (EIMS) m/z calcd for $C_{16}{}^{13}CH_{13}N_3NaO$ 299.0984 $[M + Na]^+$, found 299.0980.

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Reaction of [2-^{13}C]-Cyanoacetamide (4) with Methyl 4-(2-Oxocyclohexanecarbonyl)benzoate (12c) to Yield 3c and 8c. Performed according to General Method B: ^{13}C NMR (only signals of ^{13}C enriched C_i (**3**) and C_q (**8**) are reported) (126 MHz, $CDCl_3$) δ 99.97, 98.46; LC−MS (ESI) m/z calcd for $C_{17}{}^{13}CH_{17}N_2O_3$ 310.13 $[M + H]^+$, found 310.0 (4.85 min) and 310.0 (5.08 min); HRMS (EIMS) m/z calcd for $C_{17}{}^{13}CH_{17}N_2O_3$ 310.1267 $[M + H]^+$, found 310.1263.

Reaction of [2-^{13}C]-Cyanoacetamide (4) with 2-(4-Bromobenzoyl)cyclohexanone (12d) to Yield 3d and 8d. Performed according to General Method B: ^{13}C NMR (only signals of ^{13}C enriched C_i (**3**) and C_q (**8**) are reported) (126 MHz, $CDCl_3$) δ 100.18, 98.72; LC−MS (ESI) m/z calcd for $C_{15}{}^{13}CH_{14}BrN_2O$ 330.03/332.03 $[M + H]^+$, found 329.9/331.9 (5.44 min) and 329.9/331.9 (5.56 min); HRMS (EIMS) m/z calcd for $C_{15}{}^{13}CH_{13}BrN_2NaO$ 352.0137 $[M + Na]^+$, found 352.0139.

Reaction of [2-^{13}C]-Cyanoacetamide (4) with 2-(4-Chlorobenzoyl)cyclohexanone (12e) to Yield 3e and 8e. Performed according to General Method B: ^{13}C NMR (only signals of ^{13}C enriched C_i (**3**) and C_q (**8**) are reported) (126 MHz, $CDCl_3$) δ 100.30, 98.98; LC−MS (ESI) m/z calcd for $C_{15}{}^{13}CH_{14}ClN_2O$ 286.08 $[M + H]^+$, found 285.9 (5.35 min) and 286.0 (5.47 min); HRMS (EIMS) m/z calcd for $C_{15}{}^{13}CH_{13}ClN_2NaO$ 308.0642 $[M + Na]^+$, found 308.0628.

Reaction of [2-^{13}C]-Cyanoacetamide (4) with 2-(4-Fluorobenzoyl)cyclohexanone (12f) to Yield 3f and 8f. Performed according to General Method B: ^{13}C NMR (only signals of ^{13}C enriched C_i (**3**) and C_q (**8**) are reported) (126 MHz, $CDCl_3$) δ 100.52, 99.09; LC−MS (ESI) m/z calcd for $C_{15}{}^{13}CH_{14}FN_2O$ 270.11 $[M + H]^+$, found 270.0 (5.01 min) and 270.0 (5.13 min); HRMS (EIMS) m/z calcd for $C_{15}{}^{13}CH_{14}FN_2O$ 270.1118 $[M + H]^+$, found 270.1109.

Reaction of [2-^{13}C]-Cyanoacetamide (4) with 2-Benzoylcyclohexanone (12g) to Yield 3g and 8g. Performed according to General Method B: ^{13}C NMR (only signals of ^{13}C enriched C_i (**3**) and C_q (**8**) are reported) (126 MHz, $CDCl_3$) δ 100.30, 99.21; LC−MS (ESI) m/z calcd for $C_{15}{}^{13}CH_{15}N_2O$ 252.12 $[M + H]^+$, found 252.0 (4.92 min) and 252.0 (5.03 min); HRMS (EIMS) m/z calcd for $C_{15}{}^{13}CH_{15}N_2O$ 252.1212 $[M + H]^+$, found 252.1206.

Reaction of [2-^{13}C]-Cyanoacetamide (4) with 2-(4-Methylbenzoyl)cyclohexanone (12h) to Yield 3h and 8h. Performed according to General Method B: ^{13}C NMR (only signals of ^{13}C enriched C_i (**3**) and C_q (**8**) are reported) (126 MHz, $CDCl_3$) δ 100.33, 99.20; LC−MS (ESI) m/z calcd for $C_{16}{}^{13}CH_{17}N_2O$ 266.14 $[M + H]^+$, found 266.0 (5.26 min) and 266.0 (5.41 min); HRMS (EIMS) m/z calcd for $C_{16}{}^{13}CH_{17}N_2O$ 266.1369 $[M + H]^+$, found 266.1358.

Reaction of [2-^{13}C]-Cyanoacetamide (4) with 2-(4-Methoxybenzoyl)cyclohexanone (12i) to Yield 3i and 8i. Performed according to General Method B: ^{13}C NMR (only signals of ^{13}C enriched C_i (**3**) and C_q (**8**) are reported) (126 MHz, $CDCl_3$) δ 100.44, 99.04; LC−MS (ESI) m/z calcd for $C_{16}{}^{13}CH_{17}N_2O_2$ 282.13 $[M + H]^+$, found 282.0 (4.93 min) and 282.0 (5.13 min); HRMS (EIMS) m/z calcd for $C_{16}{}^{13}CH_{17}N_2O_2$ 282.1318 $[M + H]^+$, found 282.1322.

Reaction of [2-^{13}C]-Cyanoacetamide (4) with 2-(4-Isopropoxybenzoyl)cyclohexanone (12j) to Yield 3j and 8j. Performed according to General Method B: ^{13}C NMR (only signals of ^{13}C enriched C_i (**3**) and C_q (**8**) are reported) (126 MHz, $CDCl_3$) δ 100.38, 99.04; LC−MS (ESI) m/z calcd for $C_{18}{}^{13}CH_{21}N_2O_2$ 310.16 $[M + H]^+$, found 310.0 (5.56 min) and 310.0 (5.77 min); HRMS (EIMS) m/z calcd for $C_{18}{}^{13}CH_{21}N_2O_2$ 310.1631 $[M + H]^+$, found 310.1630.

Synthesis and Characterization of Purified Isomers ^{12}C-3a−j and ^{12}C-8a. Compounds **3a−d**, **3j**, and **8a** were synthesized with ^{12}C-cyanoacetamide, as described below. For these compounds the quaternary aromatic ^{13}C-signals proved hard to visualize with regular ^{13}C NMR analysis, even after extensive scanning of concentrated solutions. However, in the HMBC-spectra, these ^{13}C-signals are clearly visible. The reported ^{13}C-signals are therefore a result of combined ^{13}C and HMBC NMR analyses. The ^{13}C-signals obtained from the HMBC-spectra are annotated accordingly. Compounds ^{12}C-**3e−i** have been previously described by us.[6]

3-Hydroxy-1-(4-nitrophenyl)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (^{12}C-3a) and 2-Hydroxy-4-(4-nitrophenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (^{12}C-8a). In a 100 mL flask, 2-(4-nitrobenzoyl)cyclohexanone **12a** (1.0 g, 4.0 mmol) and cyanoacetamide (680 mg, 8.1 mmol) were dissolved in EtOH (30 mL). Triethylamine (1.13 mL, 8.1 mmol) was added, and the mixture was heated at reflux temperature overnight. The solvent was evaporated to yield the crude product as a solid material. From the crude product, 100 mg was washed with ice-cold EtOH (3 × 5 mL) and Et_2O (3 × 5 mL). Flash chromatography (EtOAc) on the resulting solid yielded 12 mg of ^{12}C-**3a** (0.041 mmol) and 10 mg ^{12}C-**8a** (0.034 mmol) as yellow solids. ^{12}C-**3a**: ^{1}H NMR (500 MHz, DMSO) δ (ppm) 12.59 (s, 1H), 8.33 (d, J = 8.7 Hz, 2H), 7.77 (d, J = 8.7 Hz, 2H), 2.86 (t, J = 6.5 Hz, 2H), 2.27 (t, J = 6.0 Hz, 2H), 1.78−1.68 (m, 2H), 1.62−1.52 (m, 2H); ^{13}C NMR (126 MHz, DMSO) δ 160.3 (HMBC), 159.8, 148.0, 147.8 (HMBC), 139.3 (HMBC), 130.7, 123.5, 115.6, 114.6 (HMBC), 99.6, 29.0, 24.9, 21.8, 20.9; LC−MS 5.06 min, LC-purity > 99%; HRMS (EIMS) m/z calcd for $C_{16}H_{12}N_3O_3$ 294.0884 $[M - H]^-$, found 294.0874. ^{12}C-**8a**: ^{1}H NMR (500 MHz, DMSO) δ (ppm) 12.56 (s, 1H), 8.37 (d, J = 8.7 Hz, 2H), 7.67 (d, J = 8.7 Hz, 2H), 2.65 (t, J = 6.3 Hz, 2H), 2.00 (t, J = 6.1 Hz, 2H), 1.73−1.64 (m, 2H), 1.61−1.51 (m, 2H); ^{13}C NMR (126 MHz, DMSO) δ 159.8, 159.6, 151.0, 147.9, 142.1, 129.4, 123.9, 115.8, 111.9, 100.1, 27.3, 24.7, 21.7, 20.5; LC−MS 4.89 min, LC-purity 98%; HRMS (EIMS) m/z calcd for $C_{16}H_{12}N_3O_3$ 294.0884 $[M - H]^-$, found 294.0881.

1-(4-Cyanophenyl)-3-hydroxy-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (^{12}C-3b). In a 100 mL flask, crude 4-(2-oxocyclohexanecarbonyl)benzonitrile **12b** (5.07 g, 22 mmol), which was synthesized as previously described,[6] and cyanoacetamide (2.79 g, 33 mmol) were dissolved in EtOH (50 mL) by applying brief heating. After cooling to room temperature, triethylamine (3.1 mL, 22 mmol) was added, and the mixture was stirred at room temperature for 24 h. The precipitated solid was filtered, washed with cold EtOH and recrystallized from EtOH to yield 860 mg ^{12}C-**3b** (3.1 mmol, 10%) as a yellow solid: mp 281.1−283.9 °C; ^{1}H NMR (500 MHz, DMSO) δ (ppm) 12.54 (s, 1H), 7.99 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H), 2.84 (t, J = 6.5 Hz, 2H), 2.25 (t, J = 6.1 Hz, 2H), 1.76−1.68 (m, 2H), 1.61−1.53 (m, 2H); ^{13}C NMR (126 MHz, DMSO) δ 160.3 (HMBC), 159.8, 148.2 (HMBC), 136.9 (HMBC), 132.4, 130.0, 118.4, 115.6, 113.6 (HMBC), 112.4, 100.8 (HMBC), 29.0, 24.9, 21.8, 20.9; LC−MS 4.85 min, LC-purity 98%; HRMS (EIMS) m/z calcd for $C_{17}H_{12}N_3O$ 274.0986 $[M - H]^-$, found 274.0973.

Methyl 4-(4-cyano-3-hydroxy-5,6,7,8-tetrahydroisoquinolin-1-yl)benzoate (^{12}C-3c). In a 100 mL flask, methyl 4-(2-oxocyclohexanecarbonyl)benzoate **12c** (500 mg, 1.9 mmol) and cyanoacetamide (323 mg, 3.8 mmol) were dissolved in MeOH (50 mL). Triethylamine (535 μL, 3.8 mmol) was added, and the mixture was heated at reflux temperature for four days. After evaporation of most of the solvent, 100 mg of the precipitated solid material was collected and purified using flash chromatography (1:1 EtOAc/Heptane) to yield 16 mg ^{12}C-**3c** (0.05 mmol) as a white solid: ^{1}H NMR (500 MHz, DMSO) δ (ppm) 12.53 (s, 1H), 8.05 (d, J = 8.3 Hz, 2H), 7.61 (d, J = 8.3 Hz, 2H), 3.89 (s, 3H), 2.84 (t, J = 6.5 Hz, 2H), 2.26 (t, J = 6.3 Hz, 2H), 1.76−1.68 (m, 2H), 1.60−1.52 (m, 2H); ^{13}C NMR (126 MHz, DMSO) δ 165.8, 160.9 (HMBC), 159.8, 148.2 (HMBC), 136.9 (HMBC), 130.6, 129.5, 129.2, 115.8, 113.6 (HMBC), 100.8 (HMBC), 52.5, 29.0, 25.0, 21.8, 20.9; LC−MS 5.09 min, LC-purity 95%; HRMS (EIMS) m/z calcd for $C_{18}H_{15}N_2O_3$ 307.1088 $[M - H]^-$, found 307.1081.

1-(4-Bromophenyl)-3-hydroxy-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (^{12}C-3d). In a 50 mL flask, 2-(4-bromobenzoyl)-cyclohexanone **12d** (300 mg, 1.1 mmol) and cyanoacetamide (179 mg, 2.1 mmol) were dissolved in EtOH (25 mL). Triethylamine (297 μL, 2.1 mmol) was added, and the mixture was heated at reflux for two days. The reaction mixture was cooled to room temperature. The solid material was filtered and washed with ice-cold EtOH (3 × 2 mL) and Et_2O (3 × 2 mL) to yield 180 mg ^{12}C-**3d** (0.54 mmol, 51%): ^{1}H NMR

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(500 MHz, DMSO) δ (ppm) 12.45 (s, 1H), 7.71 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 2.83 (t, J = 6.5 Hz, 2H), 2.27 (t, J = 6.2 Hz, 2H), 1.77−1.66 (m, 2H), 1.62−1.51 (m, 2H); ^{13}C NMR (126 MHz, DMSO) δ 160.6 (HMBC), 159.9, 148.6 (HMBC), 132.4 (HMBC), 131.4, 131.1, 123.4, 115.8, 113.6 (HMBC), 100.2 (HMBC), 29.0, 25.0, 21.9, 20.9; LC−MS 5.55 min, LC-purity >99%; HRMS (EIMS) m/z calcd for $C_{16}H_{12}BrN_2O$ 327.0138 $[M - H]^-$, found 327.0136.

1-(4-Chlorophenyl)-3-hydroxy-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (^{12}C-3e). This compound has been described by us previously.[6]

1-(4-Fluorophenyl)-3-hydroxy-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (^{12}C-3f). This compound has been described by us previously.[6]

3-Hydroxy-1-phenyl-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (^{12}C-3g). This compound has been described by us previously.[6]

3-Hydroxy-1-*p*-tolyl-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (^{12}C-3h). This compound has been described by us previously.[6]

3-Hydroxy-1-(4-methoxyphenyl)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (^{12}C-3i). This compound has been described by us previously.[6]

3-Hydroxy-1-(4-isopropoxyphenyl)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (^{12}C-3j). In a 50 mL flask, 2-(4-isopropoxybenzoyl)cyclohexanone **12j** (200 mg, 0.8 mmol) and cyanoacetamide (129 mg, 1.5 mmol) were dissolved in EtOH (20 mL). Triethylamine (214 μL, 1.5 mmol) was added, and the mixture was heated at reflux for four days. The reaction mixture was cooled to room temperature, and the solid material was filtered. Thirty milligrams of the crude material was washed with ice-cold EtOH (3 × 2 mL) and Et_2O (3 × 2 mL). The remaining solid was recrystallized from EtOH to yield 14 mg ^{12}C-**3j** (0.045 mmol) as a yellow solid: mp 293.1−295.4 °C; ^{1}H NMR (500 MHz, DMSO) δ (ppm) 12.28 (s, 1H), 7.37 (d, J = 8.7 Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 4.74−4.65 (m, 1H), 2.82 (t, J = 6.5 Hz, 2H), 2.32 (t, J = 6.2 Hz, 2H), 1.77−1.67 (m, 2H), 1.60−1.52 (m, 2H), 1.29 (d, J = 6.0 Hz, 6H); ^{13}C NMR (126 MHz, DMSO) δ 160.4 (HMBC), 160.0, 158.6, 149.7 (HMBC), 130.6, 124.3 (HMBC), 116.1, 115.1, 113.1 (HMBC), 99.5 (HMBC), 69.4, 29.0, 25.3, 22.0, 21.8, 21.0; LC−MS 5.56 min, LC-purity >99%; HRMS (EIMS) m/z calcd for $C_{19}H_{19}N_2O_2$ 307.1452 $[M - H]^-$, found 307.1444.

Semiempirical MO Calculations. Starting materials **12** were subjected to a stochastic conformational search using MOE2011.10 to find the global minimum structures (forcefield: MMFF94x, rejection limit = 500, energy window = 7, rms gradient = 0.005). The lowest energy conformations were used as starting point for an SCF calculation, using AM1 semiempirical method (engine = MOPAC, basis Set: AM1, solvent: none) to calculate the energies of the molecular orbitals.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for compounds **4** and **12a−j**. Quantitative ^{13}C and HMBC NMR spectra of the reaction mixtures of 2-aroyl-cyclohexanones **12a−j** with [2-^{13}C]-cyanoacetamide **4**. ^{1}H, ^{13}C, HMBC, and NOESY NMR spectra for reference compounds ^{12}**C-3a−d**, ^{12}**C-3j**, and ^{12}**C-8a**. LC−MS tracings for reference compounds ^{12}**C-3a−d**, ^{12}**C-3j**, and ^{12}**C-8a**. Cartesian coordinates and total energies of the lowest energy conformations of **12a−j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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