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On the Mechanism of the Skraup−Doebner−Von Miller Quinoline Synthesis

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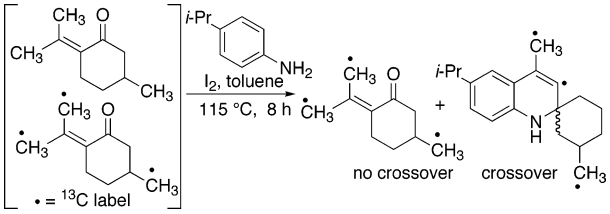
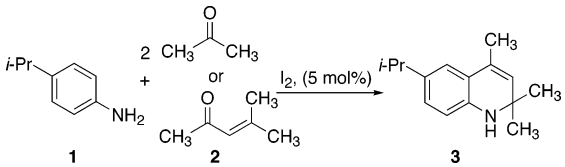


The mechanism of the formation of substituted quinolines from anilines and α,β-unsaturated ketones has been studied by the use of ^{13}C-labeled ketones in cross-over experiments. In the reaction of doubly labeled ^{13}C(2,4) mesityl oxide, a 100% scrambling of the label in the quinoline product was observed, whereas only a small (5−10%) amount of the starting mesityl oxide showed scrambling of the label. Similarly, the reaction of triply labeled pulegone clearly shows that the label in the product is 100% scrambled, whereas the label in the starting pulegone is retained. On the basis of these studies, a mechanistic pathway for the Skraup quinoline synthesis is proposed that involves a fragmentation−recombination mechanism. The aniline component condenses with the α,β-unsaturated ketone initially in a conjugate fashion, followed by a fragmentation to the corresponding imine and the ketone itself. These fragments recombine to form the quinoline product.

Introduction

The quinoline ring system is found in a myriad of naturally occurring as well as medicinally active synthetic drug substances. The early success of quinolines as antimalarial drugs has stimulated the development of various methods for their synthesis over the last century.[1] In addition, quinolines are present as structural subunits in metabolites derived from various flora and fauna.[2] Finally, quinolines are active components in various industrial antioxidants and dyes. Among the most general approaches to this ring system is the classic Skraup quinoline synthesis.[3] In the early 1880s, Skraup described heating a mixture of nitroethane, aniline, and glycerol with concentrated sulfuric acid to form quinoline in a very low yield.[4] Subsequently, Doebner and Von Miller replaced the glycerol with an α,β-unsaturated ketone and conducted the reaction by heating with an aromatic amine in the presence of an acid catalyst or iodine (Scheme 1).[5]

SCHEME 1



Over the last century, various modifications have been made to improve the yield and reproducibility of the Skraup quinoline synthesis. Various moderators such as acetic or boric acids, ferrous sulfate, thorium, or vanadium or iron oxides have been used to accelerate the reaction and make it higher yielding.[6] The Skraup−Doebner−Von Miller synthesis of quinolines can also be catalyzed by a number of Lewis ($SnCl_4$, $Yb(OTf)_3$, $Sc(OTf)_3$, $ZnCl_2$, $InCl_3$) and Brönsted acids (TsOH, $HClO_4$, Amberlite) in addition to iodine.[7] In addition, microwave irradia-

(1) Bradley, S. G.; Marciano-Cabral, F. Antiparasitic Drugs. In *Principles of Pharmacology*; Munson, P. L., Mueller, R. A., Breese, G. R., Eds.; Chapman & Hall: New York, 1994; Chapter 100.

(2) (a) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627−646. (b) Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 650−668.

(3) Throughout this paper, we refer to the quinoline ring systems generically to include both saturated and unsaturated derivatives.

(4) (a) Jones, G. Synthesis of the Quinoline Ring System. In *Quinolines*; Jones, G., Ed.; Wiley: New York, 1977; Chapter 2. (b) Manske, R. H. F.; Kulka, M. *Org. React.* **1953**, *7*, 59−98. (c) Skraup, Z. H. *Monatsh. Chem.* **1881**, *2*, 139−170. (d) Skraup, Z. H. *Monatsh. Chem.* **1880**, *1*, 316−318. (e) Skraup, Z. H. *Monatsh. Chem.* **1881**, *2*, 587−609. (f) Skraup, Z. H. *Ber. Dtsh. Chem. Ges.* **1882**, *15*, 897.

(5) Doebner, O.; Miller, W. V. *Ber. Dtsh. Chem. Ges.* **1881**, *14*, 2812−2817.

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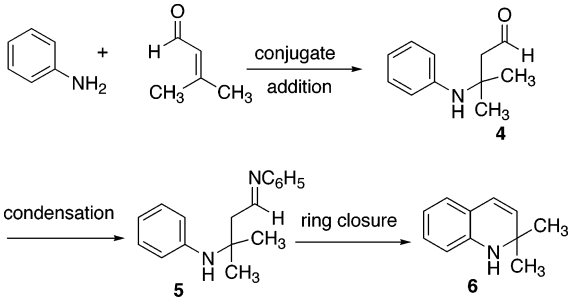
tion in combination with various Lewis acid activators has recently been employed with good results.[8] Various substituted anilines have been used in the Skraup quinoline synthesis. For ortho- and para-substituted anilines, the regiochemical outcome is unambiguous. However, the structure of the quinoline products obtained using meta-substituted anilines is unpredictable.

The easy formation of quinolines from inexpensive starting materials makes this an important synthetic reaction despite the practical shortcomings. We surmised that further improvements in the reaction yield and reproducibility would occur from a detailed understanding of the mechanism. Thus, we embarked on a mechanistic inquiry designed to answer several questions about the nature of the reactive intermediates and the timing of the bond-forming events. These studies are described in full below.

Background

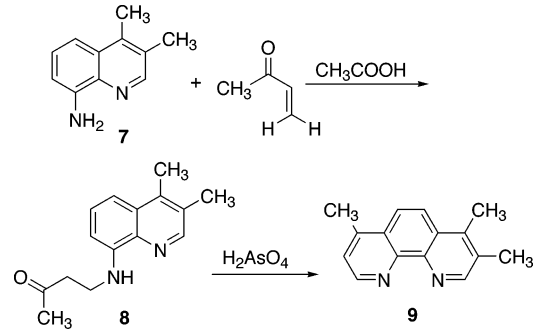
In view of the interest in the Skraup−Doebner−Von Miller quinoline synthesis, it is not surprising that many mechanistic studies are already on record. Skraup himself suggested that aldehyde anils underwent direct acid-catalyzed closure to quinolines.[4f] However, this proposal was discounted by the demonstration that 3-substituted α,β-unsaturated aldehydes afford 2-substituted quinolines. To accommodate this fact, König proposed a modification of a mechanism first suggested by Bischler which involves the 3-anilinopropanal imine **5** as the key intermediate (Scheme 2).[9] König's mechanistic proposal was subsequently supported by deuterium-labeling experiments.[10] These studies showed conclusively that anils cannot undergo direct closure but must either revert to the β-anilino carbonyl compounds and cyclize or react via the conjugate adducts (see below). However, in 1989, Eisch showed that under anhydrous conditions, in the absence of free anilines, isolated aldehyde anils undergo a rearrangement via 1,3-diazetidinium ions to afford 2-substituted quinolines.[11]

SCHEME 2



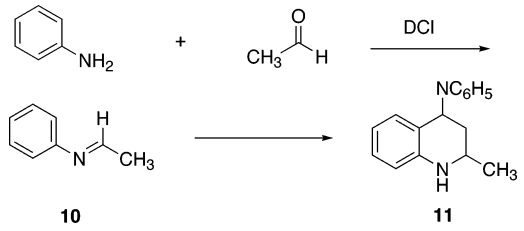
A number of different investigators provided insights into the mechanism by isolating various intermediates in the reaction sequence. For example, Badger et al. reacted 8-amino-3,4 dimethylquinoline **(7)** with methyl vinyl ketone in glacial acetic acid at room temperature to obtain *N*-(3′,4′-dimethyl-8-quinolyl)-4-aminobutane-2-one **(8),** which on heating in 80% arsenic acid forms the corresponding quinoline **9** (Scheme 3).[7f,12] This suggested that the conjugate addition is the first step in the annulation sequence.

SCHEME 3



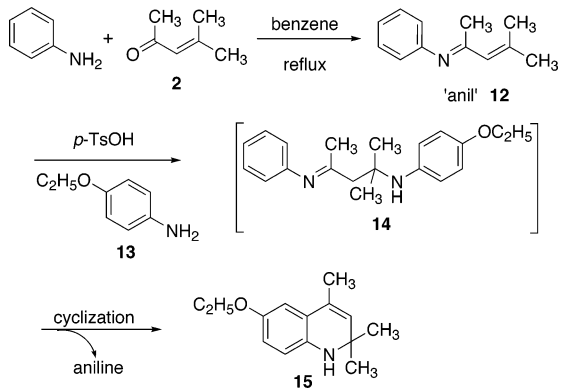
Furthermore, Dauphinee and Forrest isolated imine **10** upon treatment of aniline with acetaldehyde, which suggested that the formation of quinoline **11** proceeds by the self-condensation of a Schiff base followed by cyclization as illustrated in Scheme 4.[13]

SCHEME 4



In one of the more intriguing studies, Tung claims the isolation of various ketone anils by the treatment of aniline with mesityl oxide in boiling benzene.[14] Reaction of the anil **12** derived from aniline and mesityl oxide (**2**) with excess 4-ethoxyaniline **(13)** resulted in the formation of a quinoline derived only from 4-ethoxyaniline (Scheme 5). The formation of a single quinoline product **15** led him to speculate a

SCHEME 5



(6) (a) Cohn, B. E.; Gustavson, R. G. *J. Am. Chem. Soc.* **1928**, *50*, 2709−2711. (b) Cohn, E. W. *J. Am. Chem. Soc*. **1930**, *52*, 3685−3688. (c) Clarke, H. T.; Davis, A. W. *Org. Synth.* **1922**, *2*, 79−83. (d) Darzens, G.; Delaby, R.; Hiron, J. *Bull Soc. Chim.* **1930**, *47*, 227−232.

(7) (a) Arduini, A.; Bigi, F.; Casiraghi, G.; Casnati, G.; Sartori, G. *Synthesis* **1981**, 975−977. (b) Glinka, J. *Roczn. Chem.* **1965**, *39*, 885−893. (c) Bowers, J. S. U.S. Patent 4514570, 1985. (d) Layer, R. W.; Cuyahoga, F.; Son, P.-N. U.S. Patent 4069195, 1978. (e) Badger, G. M.; Crocker, H. P.; Ennis, B. C.; Gayler, J. A.; Matthews, W. E.; Raper, W. G. C.; Samuel, E. L.; Spotswood, T. M. *Aust. J. Chem.* **1963**, *16*, 814−827.

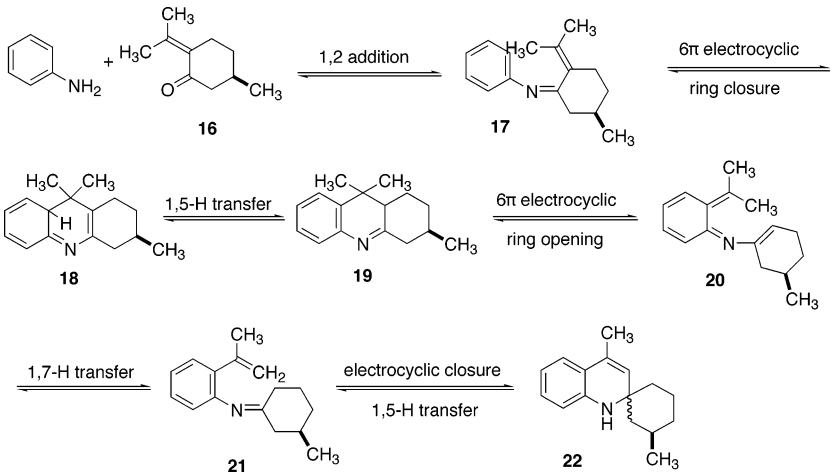
(8) (a) Theoclitou, M.-E.; Robinson, L. A. *Tetrahedron Lett.* **2002**, *43*, 3907−3910. (b) Ranu, B. C.; Hajra, A.; Dey, S. S.; Jana, U. *Tetrahedron* **59**, *59*, 813−819.

(9) (a) Bischler, A. *Ber. Dtsh. Chem. Ges.* **1892**, *25*, 2860−2879. (b) König, W. *Ber. Dtsh. Chem.* Ges **1923**, *56B*, 1853−1855.

(10) Forrest, T. P.; Dauphinee, G. A.; Miles, W. F. *Can. J. Chem.* **1969**, *47*, 2121−2122.

(11) Eisch, J. J.; Dluzniewski, T. *J. Org. Chem.* **1989**, *54*, 1269−1274.

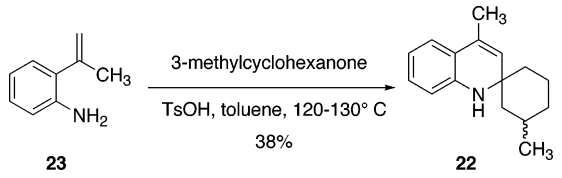
SCHEME 6



unidirectional ring closure of the intermediate **14** to form the quinoline product.

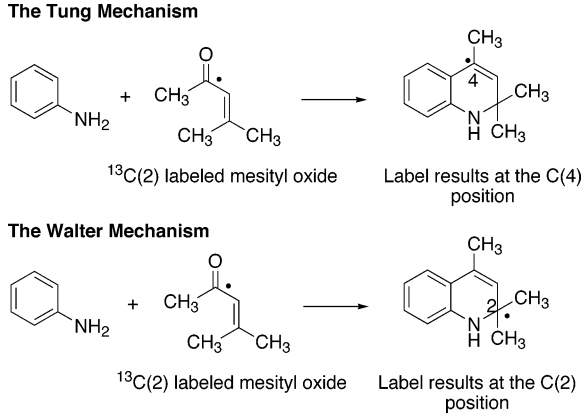
In all of the preceding studies, the direct closure of an anil to a quinoline was ruled out. However, in an intriguing series of papers, Walter observed the formation of a quinoline product from aniline and (*R*)-pulegone (**16**) whose structure could not be explained by any existing mechanistic proposals (Scheme 6).[15] To explain the formation of **22**, Walter invoked a series of electrocyclic ring closures, ring openings, and hydrogen transfers starting from anil **17** to rationalize the formation of the rearranged Skraup product. The mechanism proposed by Walter was supported by the demonstration that **23** (independently prepared) underwent a facile conversion to the expected quinoline **22** on treatment with 3-methylcyclohexanone in 38% yield (Scheme 7). Moreover, both Walter[15] and Edwards[16] have extended this observation to develop a general synthesis of 2,2-disubstituted dihydroquinolines starting from 2-alkenylanilines and carbonyl compounds.

SCHEME 7



Analysis of the mechanisms proposed by Walter and Tung (and their variants) suggested that they could be distinguished by the labeling experiment outlined in Scheme 8. If one considers the Skraup reaction of aniline with ^{13}C(2)-labeled mesityl oxide, the ^{13}C label should reside at C(4) of the quinoline according to the mechanism of Tung, Königs, and Badger. This is in line with the suggestion that the conjugate addition of aniline to α,β-unsaturated ketone or the corresponding imine leads to the product formation. However, if the Walter mechanism is operative, an experiment with ^{13}C(2)-labeled mesityl oxide would result in a quinoline having a label at the C(2) carbon from cyclization via the corresponding anil. The position of the labels could be easily established by ^{13}C NMR spectroscopy.

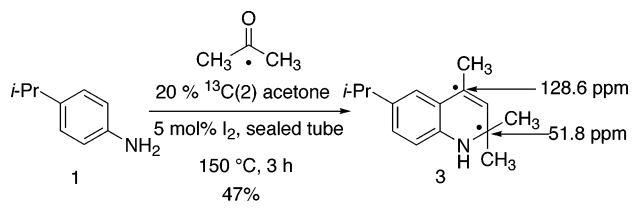
SCHEME 8



Results

1. Reaction of 4-Isopropylaniline with ^{13}C(2)-Acetone. The reaction of acetone with 4-isopropylaniline (**1**) was conducted to establish the reaction conditions and the characteristic proton and carbon resonances of the quinoline product. The choice of 4-isopropylaniline was based on the fact that the product obtained was stable and easy to purify. The reaction of 4-isopropylaniline with 5 equiv of acetone containing 20 mol % of ^{13}C(2) acetone (100% labeled) at 150 °C for 3 h in a sealed tube gave the quinoline **3** in 47% yield (Scheme 9). Two resonances were clearly enriched, thus demonstrating the incorporation of two acetone molecules to form the quinoline. Spectroscopic analysis of the product allowed the assignment

SCHEME 9



(12) (a) Badger, G. M.; Crocker, H. P.; Ennis, B. C.; Gayler, J. A.; Matthews, W. E.; Raper, W. G. C.; Samuel, E. L.; Spotswood, T. M. *Aust. J. Chem.* **1963**, *16*, 814−827. (b) Badger, G. M.; Ennis, B. C.; Matthews, W. E. *Aust. J. Chem.* **1963**, *16*, 828−832. (c) Badger, G. M.; Crocker, H. P.; Ennis, B. C. *Aust. J. Chem.* **1963**, *16*, 840−844.

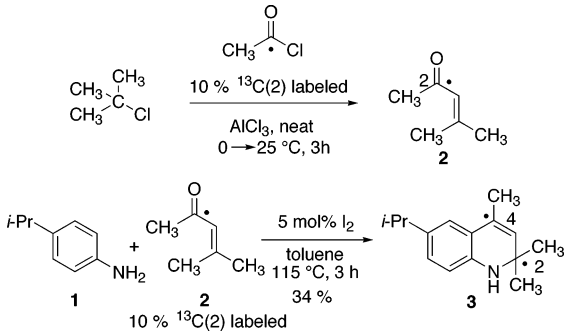
(13) (a) Forrest, T. P.; Dauphinee, G. A.; Deraniyagala, S. A. *Can. J. Chem.* **1985**, *63*, 412−417. (b) Dauphinee, G. A.; Forrest, T. P. *Can. J. Chem.* **1978**, *56*, 632−634.

(14) Tung, C. C. *Tetrahedron* **1963**, *19*, 1685−1689.

of the signal at 51.8 ppm to the ^{13}C(2) carbon and signal at 128.6 ppm to the olefinic carbon at ^{13}C(4).

2. Reaction of 4-Isopropylaniline with ^{13}C(2) Mesityl Oxide. The synthesis of ^{13}C(2)-labeled mesityl oxide was accomplished following the method of Frangopol.[17] Acetyl chloride (99% ^{13}C(1) labeled) was diluted with acetyl chloride at natural abundance such that the resultant mixture contained 10 mol % of ^{13}C(1)-labeled material. Subsequent Friedel−Crafts reaction of the acetyl chloride with *tert*-butyl chloride and anhydrous $AlCl_3$ (neat, 25°C, 3 h) afforded ^{13}C(2)-labeled mesityl oxide (**2**) in 31% yield (Scheme 10). ^{13}C NMR spectroscopic analysis revealed that the label was specifically incorporated at the C(2) position.

SCHEME 10

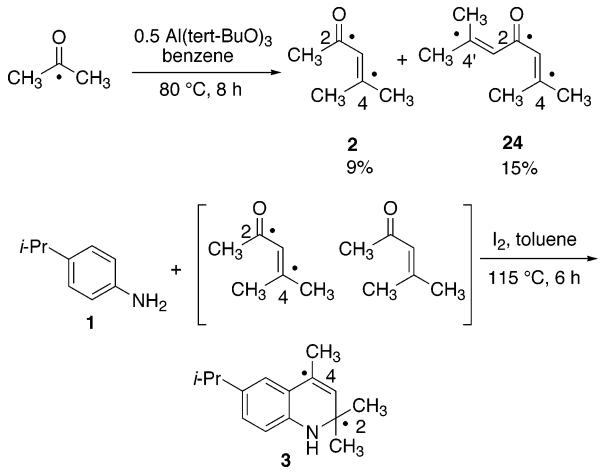


The key reaction of ^{13}C(2)-labeled mesityl oxide (**2**) was thus carried out with **1** (toluene, I_2 (mol %), reflux, 3 h) to form the quinoline **3** (Scheme 10). Spectroscopic analysis (^{13}C NMR) of **3** showed ^{13}C incorporation in *both the C(2) and C(4) positions* of the quinoline.

The surprising incorporation of the label at both the C(2) and the C(4) position of the quinoline could be explained by one of the following mechanistic scenarios: (1) the Skraup reaction proceeds by a dual mechanism and both the Tung and Walter processes are operative under the reaction conditions, (2) aniline assists in the fragmentation of mesityl oxide into component ketones which recombine to form product, or (3) mesityl oxide undergoes scrambling prior to the reaction with aniline to form the quinoline. These limiting possibilities could be distinguished with the help of double-labeled crossover experiments.

3. Double-Labeled Mesityl Oxide Crossover Experiment. A crossover experiment with double-labeled mesityl oxide would assist in deciphering whether both the Walter or the Tung mechanisms are simultaneously operative or if mesityl oxide undergoes disproportionation before the formation of quinoline. If both the Walter and Tung mechanisms were simultaneously operative, a Skraup quinoline synthesis with a equimolar mixture of double-labeled and unlabeled mesityl oxide would form the product quinoline which has a mass distribution of $M^+/(M+2)^+$ in the same ratio as the starting mixture. If aniline were assisting the fragmentation of mesityl oxide into component ketones or if mesityl oxide were scrambling prior to quinoline formation, a mass spectrometric analysis of the product would show a high $(M+1)^+$ signal. For synthetic ease, we chose to double label mesityl oxide in the C(2) and C(4) positions. The synthesis of double-labeled mesityl oxide was achieved using the method developed by Wayne and Adkins.[18] Heating a benzene solution of 99% ^{13}C(2)-labeled acetone with 0.5 equiv of freshly prepared Al(*t*-BuO)$_3$ for 8 h resulted in a green gelatinous solution. Careful chromatographic separation with ether/pentane yielded mesityl oxide (**2**) in 9% and phorone (**24**) in 15% yield (Scheme 11). Various bases such as CaO, NaOMe, and $Ti(OMe)_4$ were tried to increase the yield of the reaction, but proved disappointing.[19] Although synthetically impractical, this method yielded double-labeled mesityl oxide to conduct the double label cross over experiment. The isotopic distribution of the ^{13}C(2,4)-labeled mesityl oxide was determined using FI mass spectrometry.

SCHEME 11



The ^{13}C(2,4)-labeled mesityl oxide was diluted with mesityl oxide at natural abundance, and the Skraup quinoline synthesis with 4-isopropyl aniline was conducted in refluxing toluene. The quinoline product **3** was isolated in 47% yield, and the mass distribution of the quinoline was analyzed by FI mass spectral integration (Figure 1).

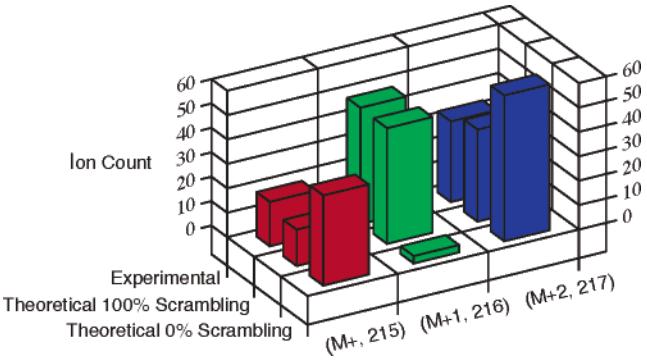


FIGURE 1. Mass spectral analysis of the quinoline product **3**.

The double-labeled mesityl oxide crossover experiment was conducted using a mixture of ^{13}C(2,4)-labeled mesityl oxide and mesityl oxide at natural abundance in a ratio of $M^+/(M+1)^+$/

(15) (a) Walter, H.; Sauter, H.; Winkler, T. *Helv. Chim. Acta* **1992**, *75*, 1274−1280. (b) Walter, H.; Sauter, H.; Schneider, J. *Helv. Chim. Acta* **1993**, *76*, 1469−1475. (c) Walter, H. *Helv. Chim. Acta* **1994**, *77*, 608−614. (d) Walter, H. *Heterocycles* **1995**, *41*, 1251−1269. (e) Walter, H. *Heterocycles* **1995**, *41*, 2427−35. (f) Walter, H. *J. Prakt. Chem.* **1998**, *340*, 309−314. (g) Walter, H.; Sundermann, C. *Heterocycles* **1998**, *48*, 1581−1591.

(16) Edwards, J. P.; Ringgenberg, J. D.; Jones, T. K. *Tetrahedron Lett.* **1998**. *39*. 5139−5142.

(17) Frangopol, M.; Genunche, A.; Negoita, N.; Frangopol, P. T.; Balaban, A. T. *Tetrahedron* **1967**, *23*, 841−844.

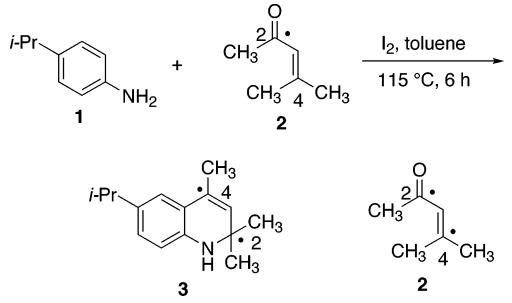
(18) (a) Wayne, W.; Adkins, H. *Org. Synth.* **1941**, *21*, 8−10. (b) Wayne, W.; Adkins, H. *J. Am. Chem. Soc.* **1940**, *62*, 3401−3404.

(19) (a) Knoevenagel, E. N.; Blach, L. *Ber. Dtsh. Chem. Ges.* **1907**, *39*, 3451−3457. (b) Hoffman, A. *J. Am. Chem. Soc.* **1909**, *31*, 722−724.

$(M + 2)^+$ 54.1%/7.5%/34.0%. The quinoline product showed a mass distribution of $M^+/(M + 1)^+/(M + 2)^+$ 33.0%/47.7%/18.2%. For the given ratio of $M^+/(M + 2)^+$ 54.1%/34.0%, the expected mass distribution for 100% scrambling would be 37.7%/47.4%/14.9%. The observed value for the product corresponds to nearly 100% scrambling. Accordingly, the Tung and Walter mechanisms are not simultaneously operating, but a mechanism must exist which requires the separation and recombination of the acetone units in mesityl oxide. However, before reaching that conclusion it was necessary to prove that mesityl oxide was not simply undergoing scrambling before incorporation into the quinoline.

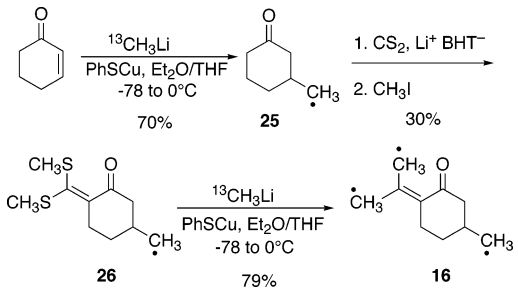
4. Scrambling of Mesityl Oxide. To test the hypothesis that the mesityl oxide underwent scrambling prior to the formation of quinoline, a control experiment was performed using ^{13}C-(2)-labeled mesityl oxide (Scheme 12).

SCHEME 12



The C(2)-labeled mesityl oxide was subjected to the conditions of the Skraup quinoline synthesis. The product and the unreacted mesityl oxide were isolated, and the extent of scrambling was qualitatively assessed by ^{13}C NMR spectroscopy. The ^{13}C spectrum of the product showed that the label was distributed among both the C(2) and C(4) position of the quinoline **3**. The analysis of the unreacted mesityl oxide showed the C(4) position was also partially enriched. However, a close inspection of the ^{13}C NMR spectra showed that the product was equally enriched in C(2) and C(4) positions, whereas the mesityl oxide was only enriched to ~10−15% at C(4). This suggested that the mechanism of scrambling of mesityl oxide was independent of that of the product. The scrambling of mesityl oxide likely arises from a slower, competitive retro aldol/aldol reaction. Even though this clearly supports the conclusion that both the Tung and Walter mechanisms are not operating simultaneously, a double-labeled crossover experiment with a more stable ketone would answer this question unambiguously.

SCHEME 13

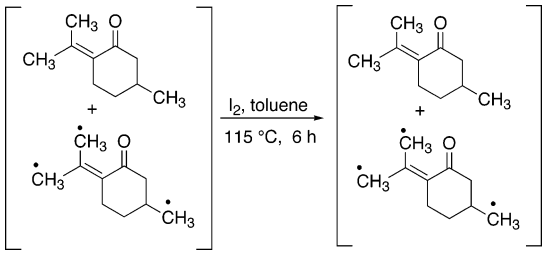


(20) Corey, E. J.; Chen, R. H. K. *Tetrahedron Lett.* **1973**, *14*, 3817−3820.

5. Synthesis of Triple-Labeled Pulegone. The experiment conducted by Walter with pulegone as the ketone resulted in the formation of the rearranged Skraup product **22**. We reasoned that pulegone may be a more stable ketone, and suitable labeling of it could assist in deciphering between the Tung and Walter mechanisms. Toward that end, pulegone was labeled at the aliphatic and the vinylic methyl groups, the two most synthetically accessible sites (Scheme 13). Labeled pulegone **(16)** was synthesized following the procedure of Corey and Chen.[20] The mixed cuprate reagent prepared from $^{13}CH_3Li$[21] and PhSCu was combined with cyclohexenone to form 3-(^{13}C)-methylcyclohexanone **(25)** in 70% yield.[22] Treatment of 3-(^{13}C)-methylcyclohexanone with Li-BHT, CS_2, and MeI produced the bismethylthio ketene acetal **26**, which underwent a second mixed cuprate methyl substitution to form the triple-labeled pulegone **(16)** in 79% yield.[23]

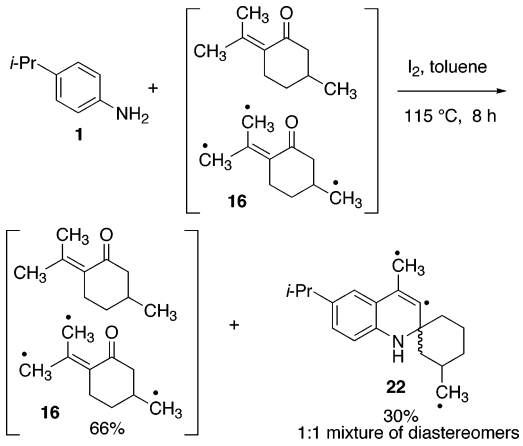
The FI mass analysis of synthetic pulegone showed an ion distribution of $M^+/(M + 1)^+/(M + 2)^+/(M + 3)^+$ 0.0%/0.0%/2.4%/87.7%. Next, the thermal stability of pulegone was established in a control experiment. Triple-labeled pulegone **(16)** was diluted with pulegone at natural abundance, and the mixture was heated to reflux in toluene with a catalytic amount of I_2 (Scheme 14). The pulegone recovered from the reaction mixture was analyzed for mass distribution by FI mass spectrometry. The mass distribution of pulegone used in the experiment was identical to the pulegone isolated from the mixture. Thus, with the knowledge that the label in the pulegone does not scramble under the Skraup reaction conditions in the absence of the amine, the triple-labeled pulegone crossover experiment could be conducted.

SCHEME 14



6. Triple-Labeled Pulegone Crossover Experiment. A mixture of pulegone with a mass distribution $M^+/(M + 3)^+$ 44.0%/45.2% was heated with 4-isopropylaniline in the presence

SCHEME 15



of 5 mol % of I_2 to form quinoline **22** in 30% yield (Scheme 15). Both of the quinoline diastereomers (1:1, 30%) and the unreacted pulegone (66%) were isolated. The distributions of the unreacted pulegone **16** and the product quinoline **22a** are shown in Figures 2 and 3.

The relative mass distribution of starting pulegone was $M^+/(M+1)^+/(M+2)^+/(M+3)^+$ 44.0%/4.2%/1.5%/45.2%. The isotopic intensities of the (M + 1) and (M + 2) peaks were very low, just 4.2% and 1.5%. The relative mass distribution of the recovered pulegone from the reaction mixture was $M^+/(M+1)^+/(M+2)^+/(M+3)^+$ 42.1%/5.7%/1.7%/46.0% (Figure 2). The mass distribution of the recovered pulegone was within experimental error (±5%) of the mass distribution in the starting pulegone. This clearly established that the pulegone is stable under the reaction conditions and no scrambling of the starting material is observed.[24]

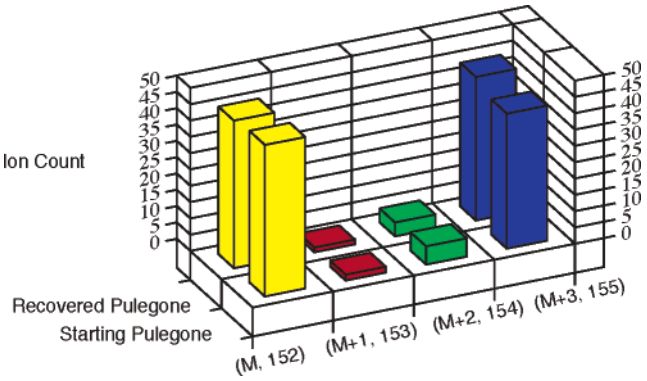


FIGURE 2. Mass spectral analysis of recovered pulegone.

7. Analysis of the Quinoline Products. As observed by Walter, the quinoline products isolated were not the normal Skraup products. The products obtained, **22a/b**, were identical to the products observed by Walter, and the two diastereomers were easily separable by silica gel chromatography. Both of the diastereomers were independently analyzed for isotopic distribution.

The mass distribution of the quinoline product clearly shows the formation of peaks from crossover products (Figure 3). If the reaction followed either the Tung or the Walter mechanism, the mass distribution should be the same as that of the starting pulegone viz. $M^+/(M+1)^+/(M+2)^+/(M+3)^+$ 44.0%/4.2%/1.5%/45.2%. The distribution of the ^{13}C label in the product quinolines was $M^+/(M+1)^+/(M+2)^+/(M+3)^+$ 19.7%/25.3%/26.2%/28.8% for the nonpolar diastereomer and 21.9%/25.6%/25.4%/27.1% for the polar diastereomer. These are similar to the mass distribution obtained for 100% theoretical scrambling which is $M^+/(M+1)^+/(M+2)^+/(M+3)^+$ 24.2%/25.0%/25.0%/25.9%. The result of complete scrambling of the label in the quinoline product together with the unscrambled label in the recovered pulegone demonstrates clearly that the pulegone dissociates irreversibly into the corresponding ketone fragments before incorporation into the quinoline nucleus.

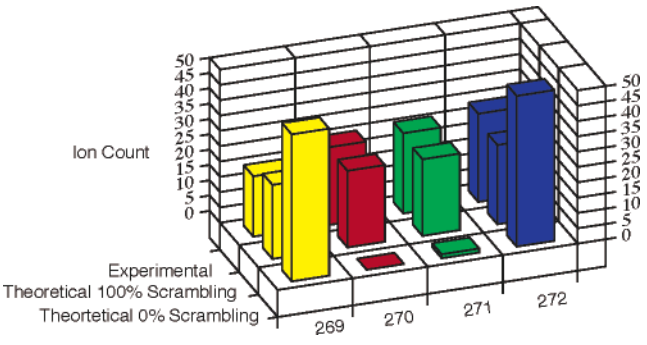
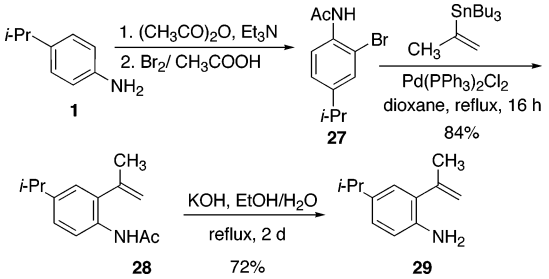


FIGURE 3. Mass spectral analysis of quinoline product **22a** (more polar diastereomer).

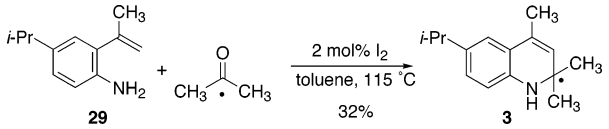
8. Reaction of 2-Isopropenyl-4-isopropylaniline (29). The synthesis of 2-isopropenyl-4-isopropylaniline was accomplished as shown in Scheme 16. 4-Isopropylaniline was protected as the acetanilide which was then brominated in acetic acid to afford **27**.[25] The bromide was cross-coupled with 2-ispropenyltributylstannane using $PdCl_2(PPh_3)_2$ to afford anilide **28**.[26] Hydrolysis of the acetamide group in **28** was accomplished in refluxing alcoholic KOH to yield 2-isopropenyl-4-isopropylaniline **(29)**.[27]

SCHEME 16



Aniline **29** was tested for its ability to undergo the Skraup quinoline synthesis following Walter's precedent. Heating **29** with 20% $^{13}C(2)$-enriched acetone under the conditions described by Walter afforded the expected quinoline **3** in 32% yield (Scheme 17). Thus, **29** is indeed capable of undergoing the Skraup quinoline synthesis. However, the yield of the product obtained was lower than that obtained in the reaction of 4-isopropylaniline with acetone, and a substantial amount of a secondary product of the quinoline with the starting aniline was observed.

SCHEME 17



Discussion

The labeling experiments conducted above clearly demonstrate that for hindered ketones such as mesityl oxide or pulegone direct cyclization of (1) an intermediate from conjuga-

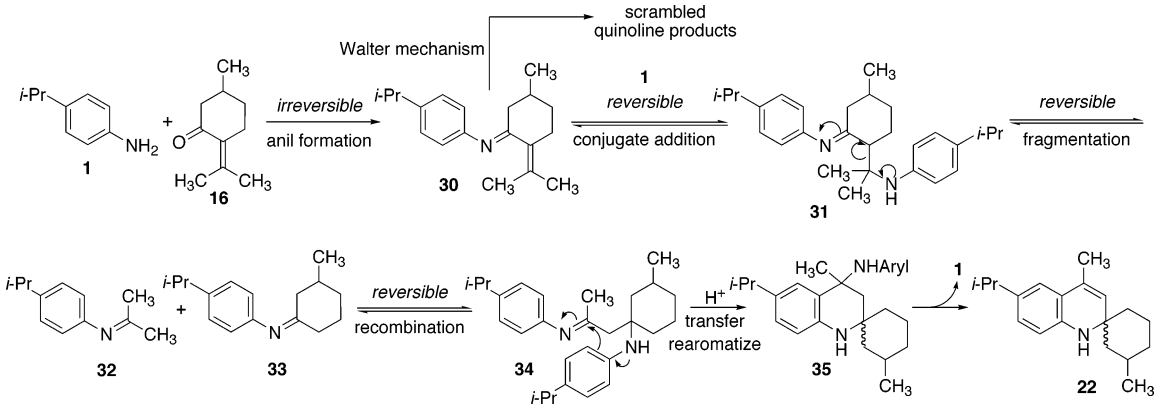
(21) Oppolzer, W.; Mirza, S. *Helv. Chim. Acta* **1984**, *67*, 730−738.

(22) (a) Adams, R.; Reifschneider, W.; Ferretti, A. *Org. Synth.* **1962**, *42*, 22−25. (b) Posner, G. H.; Whitten, C. E.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 7788−7800. (c) Posner, G. H.; Whitten, C. E. *Org. Synth.* **1976**, *55*, 122−127.

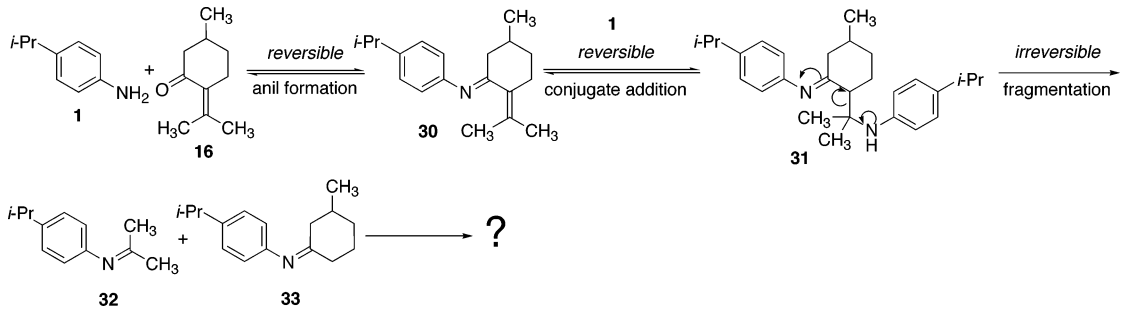
(23) (a) Dieter, R. K.; Silks, L. A. *J. Org. Chem.* **1986**, *51*, 4687−4701. (b) Dieter, R. K. *Tetrahedron* **1986**, *42*, 3029−3096. (c) Dieter, R. K.; Silks, L. A.; Fishpaugh, J. R.; Kastner, M. E. *J. Am. Chem. Soc.* **1985**, *107*, 4679−4692.

(24) A control experiment in which heating triply labeled pulegone with iodine in toluene at reflux for 8 h also showed no scrambling of the label.

SCHEME 18



SCHEME 19



tion addition, (2) the anil, or (3) a conjugate adduct of the anil is significantly slower than the fragmentation of the enones into their component ketones. Moreover, some step prior to the fragmentation must be irreversible to explain the lack of scrambling of the label in the recovered enones. This fragmentation unfortunately precludes *unambiguous* conclusions to be drawn about which of the mechanisms is operative. Nevertheless, it is instructive to consider a number of limiting mechanistic scenarios to narrow the possibilities and also as a framework for designing additional experiments to discriminate among them.

Mechanism 1: Irreversible Anil Formation. The first two mechanistic proposals invoke the initial formation of an anil. In the first scenario, the initial condensation of aniline **1** occurs in an irreversible manner to form the anil **30** Scheme 18. The anil then undergoes conjugate addition with another molecule of aniline and reversibly fragments to the component ketone imines **32** and **33**. This provides a mechanism for the scrambling of the intermediate anil. The anil may further form the quinoline following the Walter mechanism to form the quinoline products as observed. This pathway allows for the scrambling of the product and recovery of the starting material unscrambled. However the assumption that the "anil" is formed irreversibly is contrary to the conventional wisdom. Moreover, the fragmentation of **31** into imines **32** and **33** in a reversible reaction requires the observation of other quinoline products. In addition, there is no obvious reason that **34** undergoes cyclization to form a quinoline, if **31** cannot. Thus, irreversible formation of anil **30** is discarded on the basis of these two inconsistencies.[28]

Mechanism 2: Irreversible Fragmentation of the Anil. In this proposal, the first step is a reversible condensation of the aniline **1** with pulegone to form anil **30**, Scheme 19. The anil then undergoes a conjugate addition of another molecule of **1** in a reversible reaction to form **31**. This intermediate is then proposed to undergo an *irreversible* fragmentation into the corresponding imine fragments **32** and **33**. Although this would explain the lack of crossover in the recovered pulegone (and mesityl oxide), the *irreversible* fragmentation of **31** is illogical because the recombination is required to explain the formation of scrambled (for mesityl oxide) and rearranged (for pulegone) quinoline products. Therefore, this mechanism can be discarded.

Mechanism 3: Irreversible Formation/Fragmentation of a Conjugate Adduct. The third mechanism proposed in Scheme 20 is based on the isolation of similar intermediates by Badger et al.[12] The first step is an reversible conjugate addition of aniline to the α,β-unsaturated ketone (pulegone). Although conjugate addition of amines can be irreversible[29] (see below), the formation of a tertiary center makes this less favorable.[30] This amine intermediate **36** undergoes an irreversible fragmentation to form the acetone imine **32** and 3-methylcyclohexanone. Recombination of these two components explains the results of the labeling experiments and observation of a rearranged Skraup product.[31] The higher reactivity of the acetone imine as

(25) Sterling, E. C.; Bogert, M. T. *J. Org. Chem.* **1939**, *4*, 20−28.

(26) (a) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1−652. (b) Banwell, M. G.; Cameron, J. M.; Collis, M. P.; Crisp, G. T.; Gable, R. W.; Hamel, E.; Lambert, J. N.; Mackay, M. F.; Reum, M. E.; Scoble, J. A. *Aust. J. Chem.* **1991**, *44*, 705−728.

(27) Hock, H.; Kropf, H. *Chem. Ber.* **1956**, *89*, 2436−2438.

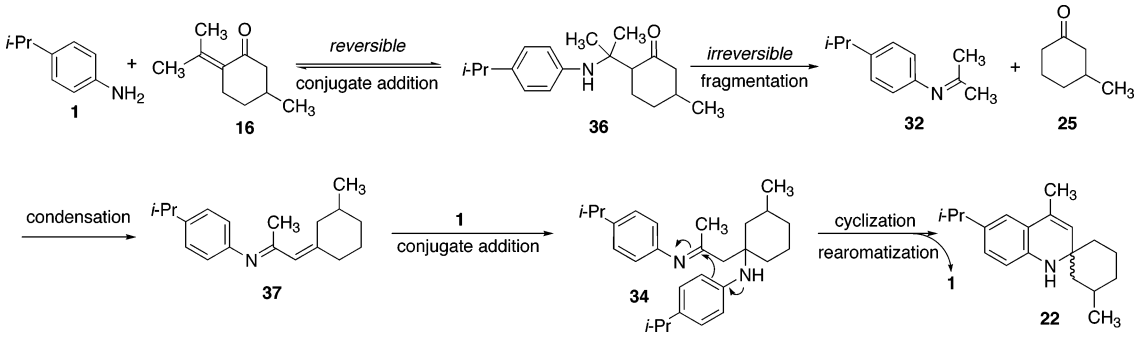
(28) A modification of this sequence wherein the formation of the anil **30** is reversible and the conjugate addition to form **31** is irreversible will lead to the same labeling results and will have the same logical inconsistencies.

(29) Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 4; Chapter 1.1.

(30) A recent study of the conjugate addition of nitrogen nucleophiles to unsaturated ketones catalyzed by Bronsted acids shows that the addition is reversible at room temperature. Wabnitz, T. C.; Spencer, J. B. *Org. Lett.* **2003**, *5*, 2141−2144.

(31) This mechanism is also allowed in the case of mesityl oxide because of a similar scrambling of labels in the product **3**.

SCHEME 20



a nucleophile in the condensation with 3-methylcyclohexanone explains the formation of a single product (albeit in low yield) and is in line with the reactivity of various enamines with aldehydes and ketones.[32] Finally, the new anil **37** suffers a conjugate addition with another molecule of aniline **1** and condenses to via **34** form quinoline **22**. A modification of this sequence wherein the first step is irreversible and the second reversible will lead to the same labeling results.[33]

The foregoing mechanism rationalizes the observation of scrambled (and rearranged) quinoline products by starting from a direct conjugate addition. Mechanisms involving initial formation of anils can also be invoked but must still account for the lack of scrambling of the label in the recovered ketones.

From the foregoing analysis, it would appear that neither the Tung nor the Walter mechanisms are operative. However, Tung's demonstration that the preformed anil of mesityl oxide forms the quinoline product in the presence of additional aniline does show that intermediates such as **33** or **35** are competent. The problem lies in explaining the unique formation of **22** from Walter's experiments (in low yield). To resolve these inconsistencies, crossover experiments should be conducted on the preformed anil **34**, thus precluding the intermediacy of **30** in mechanism 1. If no crossover is observed, then the Walter mechanism may be operative. However, this is of questionable relevance to the Skraup−Doebner−Von Miller reaction if the mechanism changes, depending upon the starting material used.

Our current view favors mechanism 3 shown in Scheme 20. This mechanism accounts for all the labeling results, can explain the unique formation of a rearranged Skraup product from pulegone, and is precedented in the studies by Badger et al. This mechanism can also explain the small amount of scrambling observed in the recovered mesityl oxide but not in the recovered pulegone. This leakage must arise from self-condensation of acetone formed from the fragmentation of the conjugate adduct (related to **36**, Scheme 20), whereas the 3-methylcyclohexanone must revert back to pulegone by additions to imines. Self-condensation leads to a different product.

Conclusions

The condensation of aniline derivatives with α,β-unsaturated ketones to form quinoline follows a complex mechanistic pathway. Our studies using labeled ketones shows that the α,β-unsaturated ketones undergo fragmentation into their corresponding ketone components. The aniline adds to the α,β-unsaturated ketone initially in a conjugate fashion, followed by a fragmentation to the corresponding imine and one of the component ketones. These fragments recombine to form an anil which leads to the quinoline product by conjugate addition of a second molecule of aniline followed by cyclization. We are presently considering studies to further distinguishing the mechanisms proposed above. We are also exploring the methods of making quinolines derived from unsymmetrical ketones in accordance with our proposal.

Experimental Section

General Experimental Procedures. See the Supporting Information.

1,2-Dihydro-6-isopropyl-2,2,4-trimethylquinoline. A solution of 4-isopropylaniline (500 mg, 3.7 mmol), mesityl oxide (725 mg, 7.3 mmol, 2.0 equiv), and iodine (10 mg, 0.037 mmol 1 mol %) in 2 mL of dry toluene was heated at reflux under N_2 for 5 h. The dark brown reaction mixture was concentrated in vacuo at 50 °C, and the crude residue was purified by silica gel chromatography (hexanes/EtOAc, 24/1) to yield the quinoline product as a clear, pale yellow liquid (303 mg, 38%).

Alternate Procedure. A solution of 4-isopropylaniline (2.0 g, 14.8 mmol) and iodine (45 mg, 0.18 mmol, 1.25 mol %) in a three-necked, round-bottom flask was attached with a Vigreux column and a distillation setup. Acetone (10 mL, 7.91 g, 136.2 mmol, 9.2 equiv) was introduced dropwise over 2 h through a second neck with a dropping funnel while the internal temperature was maintained at 150 °C. The unreacted acetone distilled out. Once the addition of acetone was complete, the reaction mixture was concentrated in vacuo and the reaction mixture was purified by silica gel chromatography (hexanes/EtOAc, 24/1) to afford the quinoline product as a colorless liquid. The chromatographed liquid was further purified by Kugelrohr distillation (1.8 g, 60%). A substantial portion of the quinoline product polymerized on distillation: bp 180 °C (0.01 mmHg, ABT); R_f 0.68 (hexane/EtOAc, 7/2); ^{1}H NMR (400 MHz) 6.93 (d, J = 1.9, 1 H, Ar-HC(7)), 6.87 (dd, J = 2.0, 7.9, 1 H, Ar HC(9)), 6.40 (d, J = 8.0, 1 H, ArHC-(10′)), 5.31 (d, J = 0.81, HC(3)), 3.6 (br s, 1 H, HN(1)), 2.80 (s, J = 6, 1 H, HC(14)), 2.01 (d, 3 H, H_3C(13)), 1.28 (s, 6 H, 2 × H_3C(12, 13)), 1.22 (d, J = 6.8, 6 H, 2 × H_3CC(15,16)); ^{13}C NMR (126 MHz) 141.24 (C(6)), 137.5 (C(8)), 128.6 (C(3)), 128.4 (C(4)), 126.1 (C(9)), 121.7 (C(7)), 121.3 (C(5)), 112.8 (C(10)), 51.8 (C(2)), 33.5 (C(14)), 31.1 (C(11,12)), 24.3 (C(15, 16)), 18.7 (C(13)); IR (neat) 3450 (s), 2958 (s), 2932 (s), 2872 (s), 1709 (s), 1492 (m), 1465 (m), 1406 (m), 1380 (m), 1328 (m), 1127 (m), 1097 (m), 1075 (m), 1011 (s), 750 (s), 700 (s); MS (EI, 70 eV) 200 ([M − CH_3]$^+$, 11), 168 (15), 158 (5), 141 (20), 128.1 (15), 115 (25), 91 (23), 77 (100), 65 (19); FI MS (150 °C) (M$^+$, 100). Anal. ($C_{15}H_{21}N$

(32) This also explains the lack of self-condensation of the ketone product which would give rise to scrambling of the label in mesityl oxide. (a) Cervinka, O. In *The Chemistry of Enamines*; Rappoport, Z., Ed.; Wiley: New York, 1994; Part 1; Chapter 9. (b) Alt, G. H.; Cook, A. G. In *Enamines*, 2nd ed.; Cook, A. G., Ed.; Dekker: New York, 1988; Chapter 4.

(33) We prefer the former proposal wherein the fragmentation is irreversible because that also helps explain why **36** does not form imine **31** and cyclize to a normal Skraup product.

(215.15)) Calcd: C, 83.73; H, 9.76; N, 6.50. Found: C, 83.73; H, 9.79; N, 6.39.

Synthesis of Quinolines 22a and 22b: (3*R*)-6′-Isopropyl-3,4′-dimethylspiro[cyclohexane-1,2′(1′*H*)-quinoline]. A solution of 4-isopropylaniline (0.50 g, 3.70 mmol), (*R*)-pulegone (0.70 g, 4.625 mmol, 1.25 equiv, technical grade), and iodine (19 mg, 0.08 mmol 2 mol %) was heated to reflux in toluene (5.0 mL) for 13 h. The dark brown solution was concentrated in vacuo, and the residue was purified by silica gel chromatography (hexanes/ether 6/1) to provide 206 mg (21%) of **22a** and 200 mg (20%) of **22b** as pale-yellow, viscous oils. Data for **22a**: $R_f = 0.69$ (hexane/ether, 6/1); $[\alpha]_D$ −51.3 ($c = 1.05$, $CHCl_3$); ^{1}H NMR (500 MHz, methanol-d_4) 6.87 (d, 1 H, $J = 2.0$ Hz), 6.82 (dd, 1 H, $J = 2.0$, 8.0 Hz), 6.59 (d, 1 H, $J = 8.0$ Hz), 5.18 (d, 1 H, $J = 1.5$ Hz), 2.74 (h, 1 H, $J = 7.0$ Hz), 1.95 (d, 3 H, $J = 1.5$ Hz), 1.91−1.85 (m, 2 H), 1.69−1.52 (m, 4 H), 1.17 (d, 6 H, $J = 6.9$ Hz), 1.14−1.11 (dq, 1 H, $J = 4.4$, 13.7 Hz), 0.85 (d, 3 H, $J = 6.4$ Hz), 0.87−0.80 (m, 2 H); ^{13}C NMR (126 MHz, methanol-d_4) 141.3, 137.7, 129.9, 128.9, 125.5, 122.6, 120.8, 113.6, 53.1, 45.7, 36.1, 34.0, 33.4, 26.3, 23.4, 21.8, 20.0, 17.4; IR (KBr, cm^{-1}) 3409 (m), 3018 (m), 2951 (s), 2940 (s), 2921 (s), 2918 (s), 2885 (s), 2866 (s), 2844 (s), 1650 (m), 1610 (s), 1582 (s), 1500 (s), 1455 (s), 1418 (m), 1378 (m), 1361 (m), 1331 (m), 1285 (s), 1264 (m), 1203 (m), 1178 (m), 1151 (m), 1053 (m), 1046 (m), 958 (s), 885 (m), 809 (m), 645 (w), 533 (w); MS (FI) 269 (M^+, 100). Anal. ($C_{19}H_{27}N$, 269.42) Calcd: C, 84.70; H, 10.10; N, 5.20. Found: C, 84.56; H, 9.89; N, 5.08.

Data for **22b**: $R_f = 0.47$ (hexane/ether, 6/1); $[\alpha]_D$ +32 ($c = 1.52$, $CHCl_3$); ^{1}H NMR (500 MHz, methanol-d_4) 6.86 (d, 1 H, $J = 1.8$ Hz), 6.83 (dd, 1 H, $J = 2.0$, 8.2 Hz), 6.50 (d, 1 H, $J = 8.0$ Hz), 5.72 (d, 1 H, $J = 1.4$ Hz), 2.73 (h, 1 H, $J = 6.9$ Hz), 1.97 (s, 3 H), 1.99−1.95 (m, 2 H), 1.65−1.64 (m, 2 H), 1.57−1.54 (m, 2 H),1.19 (d, 6 H, $J = 7.1$ Hz), 1.20−1.13 (m, 1 H), 0.84 (d, 3 H, $J = 6.4$ Hz), 0.87−0.82 (m, 2 H); ^{13}C NMR (126 MHz, methanol-d_4) 143.3, 139.2, 130.8, 127.1, 126.7, 124.0, 122.4, 114.9, 54.6, 39.7, 35.8, 34.8, 30.1, 29.8, 23.1, 22.7, 19.2; IR (KBr, cm^{-1}) 3362 (m), 3019 (m), 2953 (s), 2949 (s), 2939 (s), 2923 (s), 2919 (s), 2888 (s), 2865 (s), 2843 (s) 1645 (s), 1610 (s), 1581 (s), 1499 (s), 1461 (s), 1455 (s), 1379 (s), 1361 (s), 1347 (s), 1331 (s), 1290 (s), 1252 (m), 1244-(m), 1219 (m), 1203 (m), 1190 (m) 1178 (m), 1151 (m), 1106 (s) 1069 (s), 1055 (s), 954(m), 884 (m), 810 (m), 646 (w), 573 (m); MS (FI) 269 (M^+, 100). Anal. ($C_{19}H_{27}N$, 269.42) Calcd: C, 84.70; H, 10.10; N, 5.20. Found: C, 84.82; H, 9.94; N, 5.30.

Acknowledgment. We are grateful to LIGAND Pharmaceuticals for financial support. We also thank Stephen Mullen for recording the mass spectra.

Supporting Information Available: Preparation and characterization of labeled **2** and **16** along with mass spectral analysis of all cross over and control experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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