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Preparation and Reactivity of Versatile α-Amino Ketones

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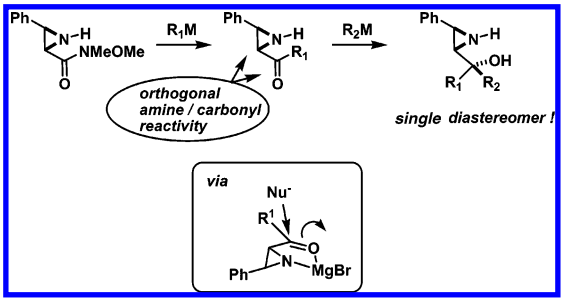

Many challenges of chemoselectivity arise from the requirement to manipulate incompatible functional groups. Synthetic methods that do not rely on protecting groups are of strategic significance to chemical synthesis. Particularly valuable are molecules with reactive functionalities that are kinetically stabilized against inter- or intramolecular reactions with each other. We have developed a simple access to molecules that contain both ketone and N−H aziridine functionalities. These compounds were found to undergo highly selective reduction and carbonyl addition reactions, making them versatile precursors to complex amines.

Introduction

Nitrogen-containing functional groups are important constituents of many biologically active molecules. The basic character of the nitrogen lone pair as well as the hydrogen bond-donating capacity of the NH group can be affected by substitution. Therefore, specificity of small molecule/biological target interactions can be modulated in complex nitrogen-containing molecules.[1] Condensations between amines and carbonyl compounds are central to the construction of such molecules. This chemistry encompasses reductive amination, enamine formation, aromatic heterocycle synthesis, and many other reactions. Unveiling the amine functionality in the presence of an aldehyde or a ketone is typically done when a condensation between them has to be initiated. Not surprisingly, an unprotected secondary amine cannot coexist with an aldehyde or a ketone within the same molecule for a prolonged period of time. Since amine and carbonyl groups are not orthogonal to each other, protection/deprotection sequences are essential (Figure 1). Our recent strategy of kinetic stabilization of amines against condensation by way of embedding the nitrogen lone pair within a strained three-membered ring provides a simple solution to the challenge of making chemically and configurationally stable amino

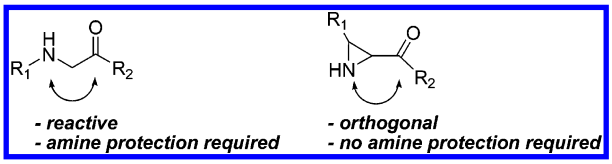

FIGURE 1. The relationship between functional groups in α-amino ketones.

aldehydes.[2] The aziridine aldehydes developed in our lab display "amphoteric" behavior in that they contain functionalities that are kinetically stabilized against inter- or intramolecular reactions with each other. They exist as dimers in the solid state and do not exhibit detectable epimerization. This finding has initiated a search for routes to other molecules that fulfill the basic requirement of amphoterism.[2] In this paper we report a new route to stable ketone-containing aziridine templates. The orthogonality between amine and ketone substituents enables highly diastereoselective transformations of the carbonyl group.

Results and Discussion

Aziridine-2-carboxylate esters were chosen as starting materials. These molecules are either commercially available or easy

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(2) Hili, R.; Yudin, A. K. *J. Am. Chem. Soc.* **2006**, *128*, 14772.

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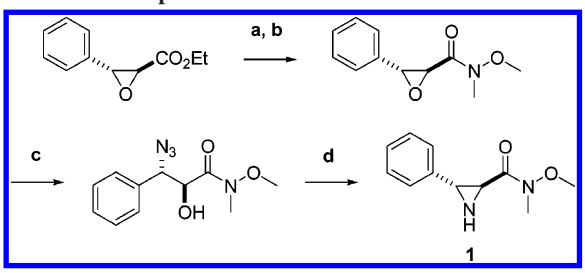
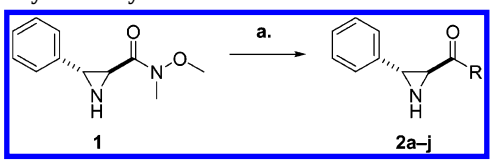
SCHEME 1. Preparation of Amide 1[a]



[a] Reagents and conditions: (a) 1.3 equiv of KOH, EtOH; (b) 1.0 equiv of DCC, 1.0 equiv of $HCl{\cdot}NH(CH_3)OCH_3$, CH_2Cl_2, rt; 60% over two steps; (c) 3.0 equiv of NaN_3, 3.0 equiv of NH_4Cl, MeOH, reflux; (d) 1.05 equiv of PPh_3, CH_3CN, reflux; 71% over two steps.

SCHEME 2. Addition of Organometallic Reagents to *N*-Methoxy-*N*-methyl-2-aziridinecarboxamides[a]



[a] Reagents and conditions: (a) RLi or RMgX (2.5 eqiv), THF, −78 °C or 0 °C → room temperature.

to prepare from the corresponding hydroxyl amino esters, azido esters, α-halo-*β*-amino esters, olefins, imines, or aldehydes.[3] Grignard additions to aziridine-2-carboxylate esters resulted in mixtures of alcohols and ketones. We therefore considered converting the ester moiety into the Weinreb amide.[4] Due to the acid-sensitive nature of aziridines, the ring opening of the aziridine ring by chloride anion was observed in our first attempt to prepare the corresponding hydroxylamides.[5] Gratifyingly, simple reversal of the sequence of amide formation and aziridine ring-closure steps resulted in a clean formation of the aziridine Weinreb amide.[6]

To prepare 2-ketoaziridines, we explored the addition of organometallic reagents to **1**. We were able to obtain the ketone products in up to 91% yields (Scheme 2 and Table 1). Contrary to aziridine aldehydes,[2] dimerization of aziridine ketones did not take place. The scope of this process was extended to alkyl and aromatic ketones by employing either the iodine−magnesium exchange protocol described by Knochel[7] or directed ortho-metalation.[8] The high isolated yields of alkyl-substituted ketones are particularly noteworthy. Prior to our work, the routes to ketone-containing aziridines have been based on addition/elimination sequences with NH_2−X (X: leaving group) reagents and α,*β*-unsaturated ketones. This chemistry is restricted to aryl ketones and does not work with enolizable substrates.[3,9]

TABLE 1. Preparation of Aziridine Ketones

Entry	Nucleophile	Product	Yield
1	MeLi	**2a**	84%
2	^{i}PrMgCl	**2b**	76%
3	^{n}BuLi	**2c**	91%
4	MgBr	**2d**	70%
5	MgX	**2e**	69%[a]
6	MgX, OCH_3	**2f**	66%[a]
7	H_3CO, MgX	**2g**	67%[a]
8	MgX, H_3CO	**2h**	78%[a]
9	MgX, F	**2i**	31%[a]
10	Li, OMOM	**2j**	68%[b]
11	MgBr	complex mixture	
12	MgBr	decomposition	
13	Me_3Si—≡—Li	decomposition	
14	MgCl	complex mixture	

[a] Grignard reagents were prepared by iodine−magnesium exchange with isopropylmagnesium chloride. [b] Organolithium reagent was generated by ortho lithiation.

When using unsaturated organometallic reagents such as allyl-, vinyl-, or ethynylmagnesium halides, we observed complex mixtures of products (Table 1, entries 11−14).[9] The

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(4) (a) Singh, J. *J. Prakt. Chem.* **2000**, *342*, 340−347. (b) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815−3818.

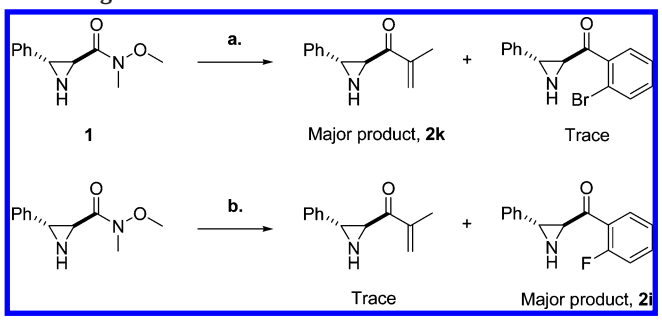
(5) Yu, L; Yudin, A. K. Unpublished results.

(6) For examples of synthesis of *N*-protected aziridine Weinreb amides see: (a) Molander, G. A.; Stengel, P. J. *Tetrahedron* **1997**, *53*, 8887−8912. (b) Rubin, A. E.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1997**, *36*, 2637−2640. (c) Woydowski, K.; Liebscher, J. *Synthesis* **2000**, *10*, 1444−1448. (d) Yun, J. M.; Sim, T. B.; Hahm, H. S.; Lee, W. K.; Ha, H.-J. *J. Org. Chem.* **2003**, *68*, 7675−7680.

(7) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302−4320 and references cited therein.

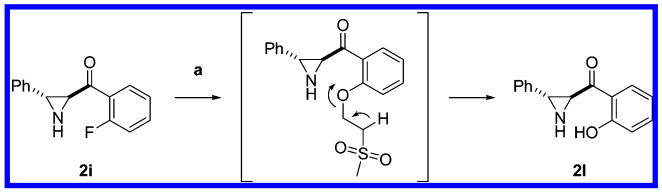
(8) (a) Hoarau, C.; Pettus, T. R. R. *Synlett* **2003**, *1*, 127−137. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879−933 and references cited therein.

SCHEME 3. Reactions between Aziridine 1 and *o*-Dihalogenated Aromatics[a]



[a] Reagents and conditions: (a) *o*-bromoiodobenzene (2 equiv), ^{i}PrMgCl (2 equiv), THF, 0 °C; (b) *o*-fluoroiodobenzene (2 equiv), ^{i}PrMgCl (2 equiv), THF, 0 °C.

SCHEME 4. Nucleophilic Aromatic Substitution in the Presence of an Unprotected Aziridine[a]



[a] Reagents and conditions: (a) 1.5 euiv of methylsulfonylethanol, 4.0 equiv of NaH, DMF; 71%.

corresponding side reactions, such as intermolecular conjugate addition of aziridines, may account for the difficulties in isolation.[10]

When *o*-bromoiodobenzene was used, the unexpected α,β-unsaturated ketone **2k** was isolated as the main product. However, with *o*-fluoroiodobenzene as the starting material, the desired ketone predominated (Scheme 3). By limiting the reaction time to 30 min, we were able to selectively obtain **2i** along with recovered starting material (Table 1, entry 9).

When treated with methylsulfonylethanol under basic conditions,[11] the aryl fluoride **2i** underwent chemoselective nucleophilic aromatic substitution producing the phenol **2l** (Scheme 4). This example attests to the stability of N−H aziridine-containing ketones under basic conditions: the aziridine ring in **2l** resists ring-opening, enabling chemoselective transformation at the periphery of the molecule.

With the ketoaziridines in hand, their participation in carbonyl addition chemistry was evaluated. We hypothesized that upon deprotonation, the NH group may facilitate chelative interactions with metal-based nucleophiles. In the event, both **2g** and **2h** were reduced to the corresponding secondary alcohols with sodium borohydride or lithium aluminum hydride (Scheme 5).[12] Interestingly, the reduction was found to produce a single diastereomer: the structure of aziridinemethanol **3g** was established by X-ray crystallography. The product stereochemistry is consistent with a chelation-control model. Previous examples

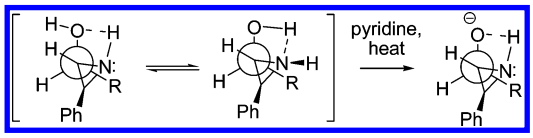
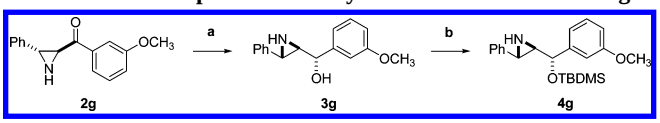


FIGURE 2. Hydrogen bonding in aziridinemethanols.

SCHEME 5. Preparation of Silylated Aziridine Alcohol 4g[a]



[a] Reagents and conditions: (a) $NaBH_4$, methanol:dioxane 2:1, 67%; or $LiAlH_4$, THF, 79%; (b) TBDMSCl, DMAP, CH_2Cl_2, 87%.

of the reduction of *N*-alkyl-2-ketoaziridines have shown wide variability in the degree and sense of diastereoselection, and dependence upon the substrate and reducing agent,[13] which mirrors the situation with 2-ketoepoxides.[14]

The molecule **3g** contains an interesting array of functional groups. NMR spectroscopic characterization of **3g** in both $CDCl_3$ and DMSO-d_6 was complicated by the presence of several broad, unresolved resonances attributed to the aziridine and alcohol methine protons. Addition of 1 equiv of pyridine to a sample in DMSO-d_6 improved resolution.[15] This observation reflects a dynamic equilibrium between the conformational isomers attributable to the slow (on the NMR time scale) inversion at the aziridine nitrogen.[16] The effect of heating the alcohol with pyridine likely comes about by deprotonation, resulting in a rigid hydrogen-bonded five-membered ring, in which the aziridine nitrogen does not undergo inversion (Figure 2). The ^{1}H NMR signals that were broad, but distinctly assignable to the product methine protons, were observed when using methanol-d_4 as the solvent. Not unexpectedly, the rate of inversion at nitrogen is increased by the disruption of intramolecular hydrogen bonding in methanol. Gratifyingly, the *O-tert*-butyldimethylsilyl derivatives (Scheme 5) were found to exhibit well-behaved ^{1}H NMR signals.

To further investigate the apparently strong chelation control in carbonyl additions, aryl ketone **2d** was subjected to reactions with Grignard reagents. As a result, tertiary alcohols **5a**−**c** (Scheme 6, Table 2) were formed. Initial deprotonation of the N−H aziridine moiety can be expected to result in a magnesium amide intermediate. The ensuing bidentate chelation by the aziridine amide and carbonyl oxygen to Mg^{2+} provides a clear basis for subsequent highly diasteroselective nucleophilic attack (Scheme 6). In each case the products were formed as single diastereomers. X-ray crystallographic structure determination of **5c** revealed that the reaction exclusively followed a stereochemical course consistent with the chelation control model. We have assigned the structures of **5a** and **5b** by analogy. These examples of nucleophilic addition to 2-ketoaziridines stand in contrast with the analogous transformations of 2-ketoepoxides,

(9) The complications arise from undesired condensation chemistry. For a recent example of an amine-promoted aziridination of chalcones, see: Shen, Y.-M.; Zhao, M.-X.; Xu, J.; Shi, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 8005.

(10) Gomtsyan, A.; Koenig, R. J.; Lee, C.-H. *J. Org. Chem.* **2001**, *66*, 3613−3616.

(11) Rogers, J. F.; Green, D. M. *Tetrahedron Lett.* **2002**, *43*, 3585−3587.

(12) Sasaki, M.; Yudin, A. K. *J. Am. Chem. Soc.* **2003**, *125*, 14242−14243.

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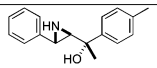
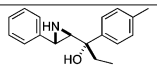
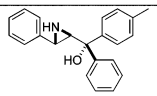
(14) (a) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191−1223. (b) Buckley, T. F.; Rapoport, H. *J. Am. Chem. Soc.* **1981**, *103*, 6157−6163.

(15) The sample was heated in an NMR tube after addition of pyridine and cooled to room temperature prior to acquiring the spectrum.

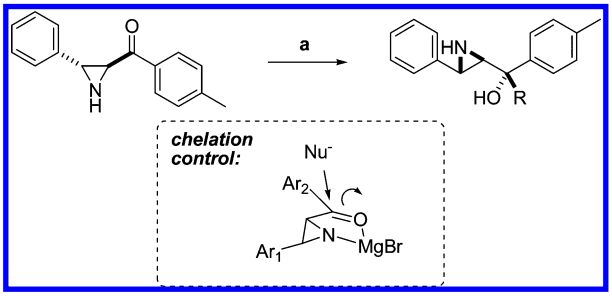
(16) Deyrup, J. A. *Chemistry of Heterocyclic Compounds*; Hassner, A., Ed.; Wiley: New York, 1983; Vol. 4, pp 1−214. The barrier to inversion in *N*-methylethylene imine is 19 kcal/mol, whereas the barrier to inversion in trimethylamine is 7.5 kcal/mol. See: Nielsen, I. M. B. *J. Phys. Chem. A* **1998**, *102*, 3193.

TABLE 2. Carbonyl Additions to Ketone 2d

Entry	Nucleophile	Product	Yield [a]
1	MeMgCl	 **5a**	74%
2	EtMgCl	 **5b**	78%
3	PhMgCl	 **5c**	56%

[a] Reactions were performed with 1.0 equiv of **2d**, 10 equiv of Grignard reagent in THF, −78→0 °C or room temperature.

SCHEME 6. Addition of Grignard Reagents to Ketone 2d[a]



[a] Reagents and conditions: (a) RMgCl, THF, −78→ 0 °C.

where chelation control relies upon the neutral epoxide oxygen.[14a] In such cases, a balance between chelation control and open-chain steric factors determines the magnitude and sense of selectivity. Carbonyl additions to *N*-protected amino ketones proceed with moderate stereocontrol.[14b] The diastereoselectivity is typically strongly substrate and condition dependent. On the other hand, Grignard additions to N−H aziridine ketones present an instance where the diastereoselectivity of nucleophilic addition is predictable by virtue of reliable chelation control involving an *anion* as one of the chelate components. This type of reaction may therefore have considerable synthetic utility for the construction of complex nitrogen-containing frameworks.

In conclusion, 2-ketoaziridines can be formed in good yields from Weinreb amides and organometallic reagents. A straightforward synthesis of aziridine-containing ketones has been developed. The orthogonal relationship between aziridine and ketone functionalities is maintained during reactions of these amphoteric compounds. The reactions of 2-ketoaziridines with hydride reducing agents and Grignard reagents were investigated, and were shown to proceed with remarkably high diastereoselectivities. The considerable synthetic utility of these molecules is currently under investigation.

Experimental Section

(±)-*trans*-*N*-Methoxy-*N*-methyl-3-phenylaziridine-2-carboxamide (1). Ethyl 3-phenylglycidate (1.0 equiv, 30 g) was sonicated in ethanol (400 mL). The mixture was cooled in an ice bath and a solution of KOH (1.3 equiv, 7.54 g) in ethanol (100 mL) was added slowly. A white solid precipitate (potassium 3-phenylglycidate) began to form, which was suction-filtered after 20 min, washed with diethyl ether, and used in the following step without further purification.

Dicyclohexylcarbodiimide (2.05 g, 10 mmol) was added to a solution of potassium 3-phenylglycidate (2.02 g, 10 mmol) in anhydrous dichloromethane (10 mL) under nitrogen at 0 °C. *N*,*O*-Dimethylhydroxylamine hydrochloride (970 mg, 10 mmol) was added, and the mixture was warmed to room temperature and stirred overnight. After 20 h, the solution was filtered and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography eluting with 5% acetone/dichloromethane, affording (±)-*N*-methoxy-*N*-methyl-3-phenyloxirane-2-carboxamide as a white gum (1.2 g, 60% from ethyl 3-phenylglycidate). This step can be performed on the 30 g scale. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38−7.31 (m, 5H), 4.09 (d, J = 1.8 Hz, 1H), 3.93 (br s, 1H), 3.72 (s, 3H), 3.28 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.5, 135.6, 128.7, 128.6, 125.8, 62.1, 57.6, 55.5, 32.6. HRMS (ESI) *m*/*z* calcd for $C_{11}H_{14}NO_3$ (MH^+) 208.0968, found 208.0976.

Sodium azide (564.4 mg, 8.68 mmol) and ammonium chloride (464.3 mg, 8.68 mmol) were added to a solution of (±)-*N*-methoxy-*N*-methyl-3-phenyloxirane-2-carboxamide (600 mg, 2.89 mmol) in methanol (20 mL). The mixture was refluxed for 5 h, concentrated by evaporation, and poured into a 1:1 mixture of ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to yield a yellow oil ((±)-(2*S*,3*S*)-3-azido-2-hydroxy-*N*-methoxy-*N*-methyl-3-phenylpropanamide), which was carried to the following step without purification. This step can be performed on the 30 g scale. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41−7.25 (m, 5H), 3.77 (d, 1H), 3.77 (s, 1H), 3.22 (s, 3H), 2.04 (m, 4H, OH + NCH_3).

Triphenylphosphine (788 mg, 3.00 mmol) was added in small portions to a stirred solution of the azido alcohol intermediate (723.3 mg, 2.89 mmol) in acetonitrile (15 mL). Evolution of nitrogen gas was observed. The mixture was stirred for 45 min at ambient temperature before refluxing for 4 h, after which no starting material remained. Product had R_f 0.27 by TLC eluting with hexanes/ethyl acetate 1:1. The solvent was evaporated in vacuo, the residue was diluted with 30% ethyl acetate/hexanes, and the precipitate of triphenylphosphine oxide was filtered. The filtrate was concentrated in vacuo and the residue purified by flash chromatography, eluting with 15% acetone/dichloromethane, to yield **1** as a pale yellow gummy solid (424 mg, 71% over two steps). This step can be performed on the 30 g scale. Mp 37.2−38.0 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32−7.25 (m, 5H), 3.69 (s, 3H), 3.28 (s, 3H), 3.11 (dd, ^3J = 7.5 Hz, ^4J = 1.8 Hz, 1H), 3.00 (d, 1H), 2.04 (t, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.4, 138.4, 128.4, 127.5, 126.1, 61.9, 40.0, 37.5, 32.8. HRMS (ESI) *m*/*z* calcd for $C_{11}H_{15}N_2O_2$ (MH^+) 207.1128, found 207.1129.

General Procedure for Addition of Organometallic Reagents to Amide 1. In a flame-dried Schlenk flask under a nitrogen atmosphere, the aryl iodide (2.8 equiv, 1.34 mmol) was dissolved in 3 mL of anhydrous tetrahydrofuran at −15 °C. Isopropylmagnesium chloride (2.8 equiv, 1.34 mmol) was added dropwise and the solution was stirred for 30 min at −15 °C. The amide (1 equiv, 0.48 mmol) was added dropwise as a solution in 0.5 mL of anhydrous tetrahydrofuran, and the reaction was allowed to warm to room temperature. After 45 min, the reaction was cooled to 0 °C, quenched with 5 mL of water, and diluted with 5 mL of ethyl acetate. The aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. The crude products were purified by flash chromatography over silica gel, eluting with 20% ethyl acetate/hexanes.

(±)-(2-Hydroxyphenyl)((2*S*,3*R*)-3-phenylaziridin-2-yl)methanone (2*l*). To a stirred solution of aryl fluoride **2i** (0.124 mmol) in 1.5 mL of dry *N*,*N*-dimethylformamide was added 2-(methylsulfonyl)ethanol (0.186 mmol), and the solution was cooled to 0 °C. Sodium hydride (0.498 mmol) was added, and the reaction mixture

was warmed to room temperature. The reaction was quenched with water and extracted with ethyl acetate and brine. The organic layer was concentrated to dryness and the crude organics purified by flash column chromatography. Yield 22.1 mg (73%). Mp 59.7 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.92 (s, 1H), 7.83−6.89 (m, 9H), 3.51 (dd, ^3J = 8.0 Hz, ^4J = 2.4 Hz, 1H), 3.22 (dd, ^3J = 9.2 Hz, ^4J = 2.4 Hz, 1H), 2.70 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.7, 162.2, 162.2, 137.9, 137.0, 137.0, 129.7, 128.6, 128.0, 126.2, 119.4, 118.5, 44.0, 43.2. HRMS (ESI) *m*/*z* calcd for $C_{15}H_{14}NO_2$ (MH^+) 240.1019, found 240.1030.

General Procedure for the Addition of Grignard Reagents to 2d. A solution of **2d** (0.2 mmol) in anhydrous tetrahydrofuran (20 mL) at −78 °C was treated with Grignard reagent (in tetrahydrofuran, 2 mmol). The reaction was warmed to 0 °C and monitored by TLC (eluent: 3:2 hexanes/ethyl acetate). The reaction was quenched with ice (1 mL) and several drops of saturated aqueous sodium bicarbonate, under vigorous stirring. The liquid phase was decanted and filtered, and the remaining solids were washed with diethyl ether. The organic phase was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography.

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Supporting Information Available: Full experimental procedures, characterization data, NMR spectra, and crystallographic information files. This material is available free of charge via the Internet at http://pubs.acs.org.

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