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Free Radical-Mediated Aryl Amination: Convergent Two- and Three-Component Couplings to Chiral 2,3-Disubstituted Indolines

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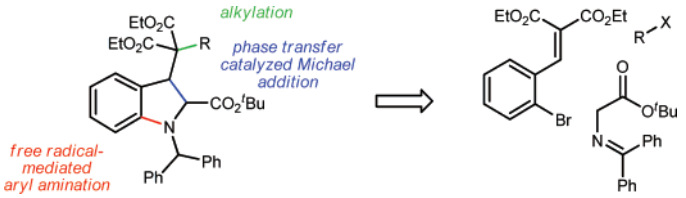
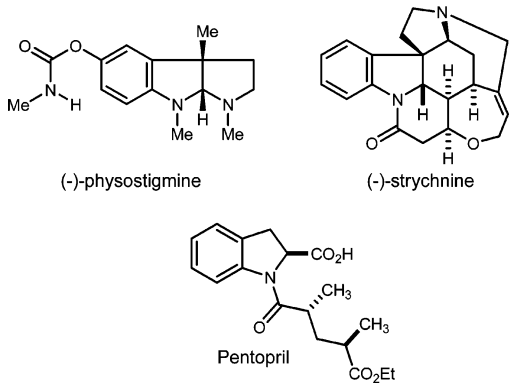


5-*exo*-*trig* Cyclization of an aryl radical to the nitrogen of an azomethine is used as the key annulating step in a modular preparation of 2,3-*cis*- and *trans*-disubstituted indolines. The precursors are readily prepared by phase-transfer-catalyzed Michael addition of a glycine Schiff base to a variety of acceptors. When the more reactive alkylidene malonate Michael acceptors are implemented, a one-pot three-component coupling is possible. The net result is a convergent [3 + 2] coupling strategy for the construction of highly functionalized indolines, a substructure occurring in numerous biologically active natural products.

Introduction

The indoline substructure is a recurring structural feature within heterocyclic alkaloid natural products (Chart 1), perhaps second only to the pyrrolidine and piperidine nitrogen heterocycles. Indoline natural products are often both structurally appealing and biologically active[4] and can range in complexity from relatively simplified fused tricycles such as physostigmine[5] to the very complex polycycles vinblastine,[6] aspidospermidine,[7] ajmaline,[8] and strychnine.[9] Indoline heterocycles are also structural components of pharmaceutical small molecules; the angiotensin converting enzyme (ACE) inhibitor Pentopril is largely built upon (*S*)-indoline-2-carboxylic acid.[10] This template has also spawned the development of "natural product like" libraries based on an aminoindoline framework.[11] Accordingly,

CHART 1. Representative Biologically Active Indoline Small Molecules



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(3) Current address: The Department of Organic Chemistry, Indian Institute of Science, Bangalore, India.
(4) Dewick, P. M. *Medicinal Natural Products—A Biosynthetic Approach*, 2nd ed.; John Wiley and Sons, Ltd.: New York, 2002.
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this structural diversity has stimulated a wide range of methods aimed at the stereoselective construction[12−14] or functionalization[15] of indoline rings. Few of these methods comprise enantioselective *annulation* methods—perhaps an indication that even modern methods remain inadequate for building certain common chiral heterocycles.[16]

We have considered the indoline annulation problem ourselves and recently reported an enantioselective indoline annulation in two steps, leading to enantioenriched 2-substituted indolines.[13] The first step of the sequence is an enantioselective phase-transfer-catalyzed glycine Schiff base alkylation.[17] Free radical-mediated aryl amination immediately follows as an enabling technology in this context, as it delivers the 2-substituted indoline under mild conditions and in protected form for further manipulation. We have since pursued a variation on this theme that targets the 2,3-disubstituted indoline ring system but retains the convergency offered by the basic modular assembly beginning from a glycine Schiff base. We report a convergent synthesis of 2,3-disubstituted indolines (Figure 1, type I, eq 1) resulting from a straightforward sequence involving conjugate addition and free radical-mediated aryl amination. Additional modularity can be obtained by slight operational change to incorporate a third component (Figure 1, type II, eq 2) by judicious choice of Michael acceptor. Both incarnations utilize the phase-transfer-catalyzed Michael addition of a protected glycine Schiff base to activated styrene derivatives.[17−19] The key annulation step is effected by a free radical reaction in which an aryl radical adds (nonconventionally) to the nitrogen of the azomethine.[13,20−23]

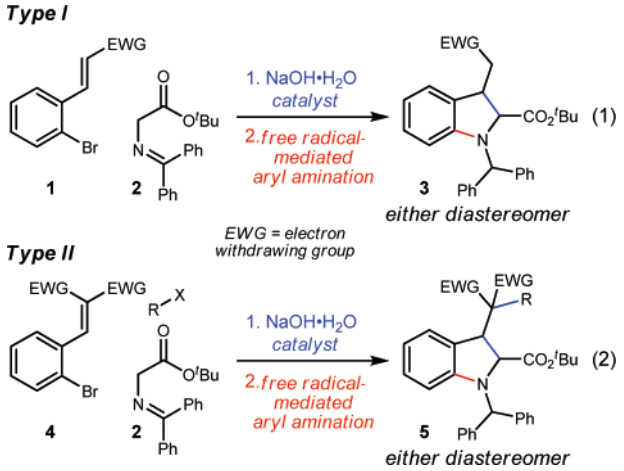

FIGURE 1. Indoline annulation via two- and three-component couplings and free radical-mediated aryl amination.

Results and Discussion

Type I: [3 + 2] Indoline Annulation via Sequential Michael Addition/Free Radical-Mediated Aryl Amination. A variety of Michael acceptors were synthesized from *o*-bromobenzaldehyde by olefination with the appropriate Wittig reagent.[24] A 6:1 *E*:*Z* ratio of (inseparable) geometric isomers of ethyl cinnamate **1a**[25] was exposed to glycine Schiff base **2**[26]

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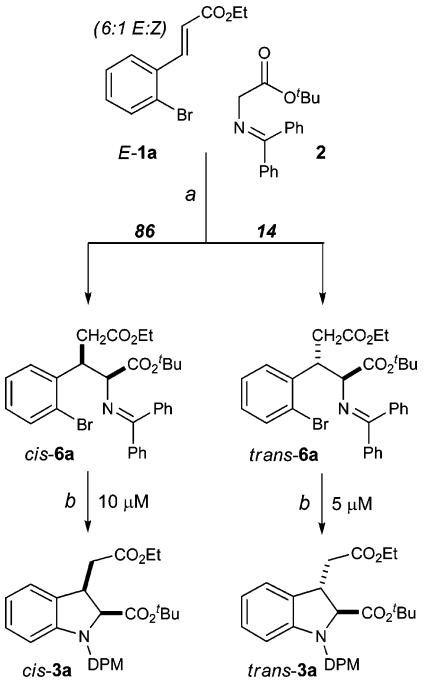
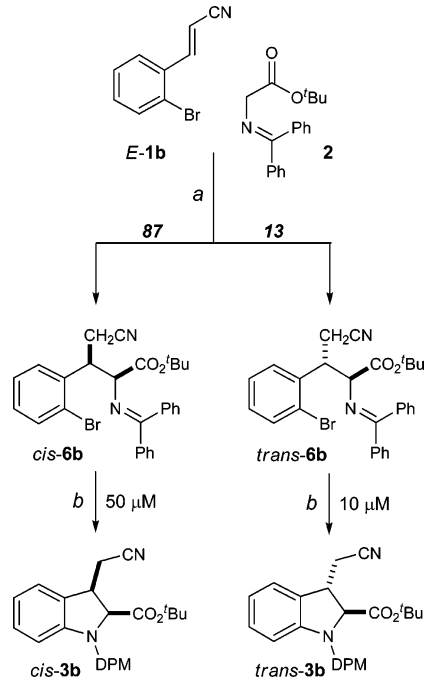
SCHEME 1. Two-Component (Type I) Indoline Synthesis from Cinnamate Precursors (Eq 1)[a]



[a] Reagents and conditions: (a) 20 mol % $BnEt_3N^+Cl^-$, 50% aq NaOH, CH_2Cl_2, 25 °C (94% from 6:1 (*E*)-**1a**:(*Z*)-**1a**); (b) $^nBu_3SnH$, AIBN, C_6H_6, 80 °C (*cis*-**3a**, 65%; *trans*-**3a**, 84%).

SCHEME 2. Two-Component (Type I) Indoline Synthesis from β-Arylacrylonitrile (Eq 1)[a]



[a] Reagents and conditions: (a) 20 mol % $BnEt_3N^+Cl^-$, 50% aq NaOH, CH_2Cl_2, 25 °C (70% from (*E*)-**1b**, 89% from (*Z*)-**1b** (58:42 dr)); (b) $^nBu_3SnH$, AIBN, C_6H_6, 80 °C (*cis*-**3b**, 61%; *trans*-**3b**, 80%).

using liquid−liquid-phase transfer conditions ($BnEt_3N^+Cl^-$, 50% aq NaOH, CH_2Cl_2) (Scheme 1). The resulting adducts were obtained as an 86:14 *cis*-**6a**:*trans*-**6a** mixture (as depicted) in a combined 94% yield. The adducts were separated by flash chromatography and individually subjected to stannane and initiator (AIBN) to effect the annulation event. Indoline *cis*-**3a** was obtained in 65% isolated yield, and the *trans*-stereoisomer was retrieved in 84% yield. The assigned stereochemistry could be confirmed at this point by NOE measurements on both diastereomers individually. Although no single example was exhaustively optimized, the different concentrations (10 vs 5 μM) for the cyclization reflect empirically determined, subtle differences in maintaining an efficient propagating radical reaction. Isolated yields may potentially be further improved by finely tuning the stannane addition rate in concert with the reaction concentration. Generally, no product of direct reduction is observed in these or subsequent examples.

Acrylonitrile derivative **1b** provided convenient access to the *cis*-adduct as well (Scheme 2). In contrast to cinnamates **1a**, the geometric isomers of nitrile **1b** were readily separated by flash chromatography, thereby allowing measurement of the impact of the olefin geometry on addition diastereoselectivity. Michael addition to β-arylacrylonitrile (*E*)-**1b** using liquid−liquid-phase transfer conditions readily occurred to provide the adduct **6b** as a separable 87:13 mixture of *cis*- and *trans*-diastereomers. Use of (*Z*)-**1b** was equally efficient (89% yield) but substantially less selective (1.4:1 *cis*:*trans*). Following chromatographic separation, the adducts **6b** were individually cyclized to indolines **3b**. Not unexpectedly, cyclization to the fully protected indoline α-amino acids *cis*-**3b** and *trans*-**3b** transpired as before in 61% and 80% yields, resepectively. Hence, 2,3-*cis*- and 2,3-*trans*-disubstituted indoline α-amino acids are readily prepared in diastereomerically pure form (>95:5) from the corresponding activated styrenes. Diastereoselection is considerably higher in additions to the (*E*)-olefins relative to their (*Z*)-isomers. These examples establish a baseline efficiency for the two-step annulation using an aryl radical cyclization to a benzophenone imine. We anticipate that this step will broadly tolerate substitution of the aryl radical on the basis of our previous studies.[13]

Type II: [3 + 2] Indoline Annulation via Sequential Michael Addition/Alkylation/Free Radical-Mediated Aryl Amination. At room temperature, the *rate* of phase-transfer-catalyzed *alkylation* is comparable to that of *Michael addition* with electrophiles **1a** and **1b**. We hypothesized that, by increasing the electrophilicity of the Michael acceptor, a sequential Michael addition/alkylation could be effected with phase-transfer catalysis in one pot. Use of alkylidene malonates **4a** allowed reduction of this strategy to practice (Figure 1, eq 2, and Table 1, eq 3).

In the absence of an alkylating agent, alkylidene malonate **4a** provided an equal amount of *cis*- and *trans*-Michael adducts **7a** (Table 1, entry 1). Addition of methyl iodide to the basic reaction mixture resulted in the desired sequence of Michael addition/malonate alkylation (Table 1, entry 2). Although the differential rates of Michael addition/alkylation enable addition of the alkylating agent at the beginning of the reaction, the process is fully optimized by adding the alkylating agent to the reaction mixture after the mixture is stirred for 3−4 h. In this way, the Michael adduct (**7b**) is obtained in 94% isolated yield. The stereoisomers were then separated and subjected to free radical conditions to complete the annulation. This step is again highly efficient, producing *cis*-**5b** and *trans*-**5b** in 80% and 93% isolated yields, respectively.

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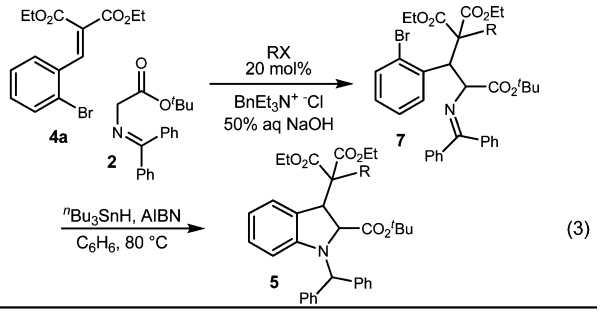
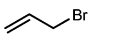
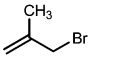
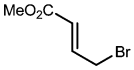
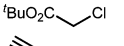
TABLE 1. Three-Component (Type II) Indoline Synthesis (Eq 3)[a]



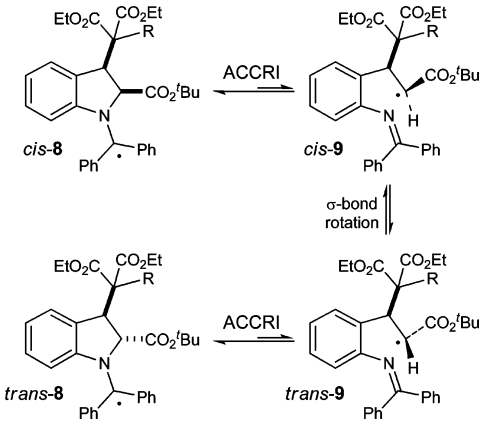
entry	R-X	Michael adduct dr (*cis*:*trans*)		yield (%)[b]	cyclization yield (%)[c] *cis*		*trans*
1	–	1:1	**7a**	90	92[d]	**5a**	83
2[e]	CH_3I	1:3	**7b**	94	80	**5b**	93
3	$PhCH_2Br$	1:1	**7c**	95			
4[f]	$PhCH_2Br$	10:1	**7c**	78	82[b]	**5c**	82[b]
5		1:1	**7d**	87	–[g]	**5d**	84
6		1:1	**7e**	95	30[d]	**5e**	78
7		2:1	**7f**	35	–[f]	**5f**	82
8		2:1	**7g**	76	45[d]	**5g**	85
9		1:1	**7h**	74	–[h]	**5h**	–[h]

[a] See the Supporting Information for complete details. Relative stereochemistry measured by NOE difference measurements. Ratios of diastereomers measured by ^{1}H NMR (400 MHz). [b] Isolated yield of both diastereomers. [c] Isolated yield. [d] Diastereomeric ratio: >20:1 *cis*-**7a** → 5:1 *cis*-**5a**; >20:1 *cis*-**7e** → 10:1 *cis*-**5e**; 10:1 *cis*-**7g** → 2:1 *cis*-**5g**. [e] A cinchonidine-derived ammonium salt was used. [f] Solid−liquid-phase-transfer conditions used: solid NaOH (20 equiv), CH_2Cl_2. [g] The indoline intermediate reacts further to unidentified products. [h] Stereo-nonselective hydrostannation is competitive with cyclization.

Alkylation of the intermediate malonate with benzyl bromide resulted in an outcome similar to that of alkylation with methyl iodide, providing the stereoisomeric Michael adducts in 95% combined yield (Table 1, entry 3). Despite the possibility of 1,5-hydrogen atom transfer from the benzylic carbon to the intermediate aryl radical, cyclization of this inseparable mixture of diastereomers furnished the cyclized products in 82% combined yield with no evidence of aryl radical direct reduction. Moreover, the adduct diastereomeric ratio could be manipulated to favor (10:1) *cis*-**7c** through the use of a solid−liquid-phase-transfer protocol (NaOH−CH_2Cl_2) (Table 1, entry 4). The high selectivity notwithstanding, a more complete picture of the reaction sequence (vide infra) was obtained by generation of both diastereomers using the nonselective liquid−liquid-phase-transfer conditions.

A variety of different malonate alkylating agents can be used (Table 1, entries 5−9). Allylation with either allyl bromide or methallyl bromide (Table 1, entries 5 and 6, respectively) proceeded to adducts **7d** and **7e** in 87% and 95% yield. In both cases, the *cis*- and *trans*-diastereomers were separable. Whereas *trans*-**7d** and *trans*-**7e** cyclized uneventfully in 84% and 78% yield, respectively, cyclization of their *cis*-counterparts was complicated by the generation of several products. Although the exact nature of these products was not ultimately determined, that aryl−nitrogen bond formation occurred was evident from the signature upfield shifts of the aromatic ring protons in the crude reaction mixture. Accordingly, adduct *cis*-**7e** in which the

SCHEME 3. ACCRI Mechanism for α-Amino Ester Epimerization during Cyclization of *cis*-Michael Adducts



vinyl group (a potential radical acceptor via addition) bears additional steric hindrance allowed isolation of *cis*-**5e** in a modest 30% yield. This behavior continued with the activated allyl derivative *cis*-**7f** (Table 1, entry 7) in which *trans*-indoline **5f** was obtained in 82% yield, but the *cis*-isomer was not formed selectively to any measurable extent. Alkylation of the Michael adduct with *tert*-butyl α-chloroacetate provided malonate derivative **7g** in 76% yield. The *cis*-isomer cyclized to *cis*-**5g** in 45% isolated yield, whereas *trans*-**7g** produced *trans*-**5g** in 85% yield (Table 1, entry 8). Although propargyl electrophiles can be sequenced in the same manner, the cyclization was accompanied by hydrostannation of the terminal alkyne. The examples in Table 1 were not individually optimized for selectivity or yield, so the results provide an indication of the generality of a standard protocol.

Selective Epimerization of the α-Amino Ester Stereocenter: Azacyclopentenyl Carbinyl Radical Isomerization (ACCRI). Several of the Michael adducts **7** exhibited a drop in diastereopurity during the indoline annulation step. While this stereochemical erosion was absent or minimal in most cases, *cis*-**7a**, *cis*-**7e**, and *cis*-**7g** were more susceptible to the isomerization, and the observation was most pronounced in the latter two. This epimerization is highly unusual since free radical conditions are exceptionally mild (pH-neutral) and tolerant of a wide range of functionality.[27]

We have previously described ACCRI in an enantioenriched indoline α-amino acid system analogous to the indolines described here.[28]

By extension of those examples in which loss of enantiomeric excess was correlated to the isomerization, loss of diastereopurity from **7** can be explained by the course of events detailed in Scheme 3. This isomerization proceeds from the radical **8** formed by aryl radical addition to the azomethine nitrogen. A key feature of the isomerization is the nucleophilic nature of **8** and the electrophilic character of **9**, which, in concert, lower the activation barrier via a polarization effect.[29] Using conditions that allow isomerization to compete with direct hydrogen atom transfer to **8** (low effective stannane concentration), the *cis*-

(27) For leading references to epimerization of unactivated C−H bonds, see: Tanner, M. E.; Kenyon, G. L. In *Comprehensive Biological Catalysis*; Sinnott, M., Ed.; Academic Press: San Diego, 1988; Vol. 2. Frey, P. A. *Chem. Rev.* **1990**, *90*, 1343.

(28) Viswanathan, R.; Mutnick, D.; Johnston, J. N. *J. Am. Chem. Soc.* **2003**, *125*, 7266.

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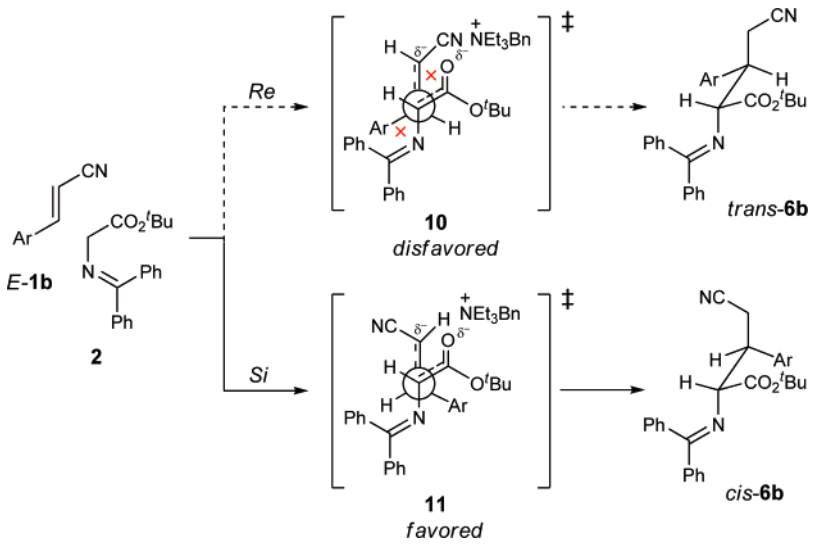


FIGURE 2. Proposed competing transition states for (*E*)-olefin acceptors to rationalize *syn*-selectivity.

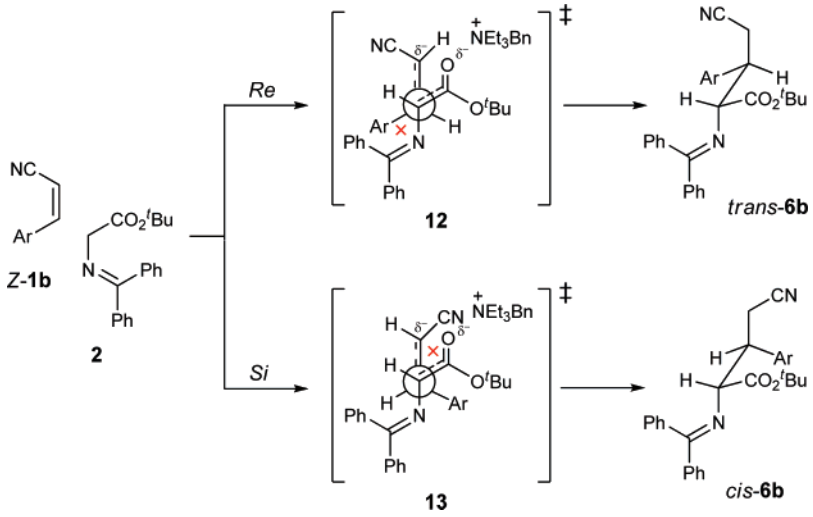


FIGURE 3. Proposed competing transition states for (*Z*)-olefin acceptors to rationalize low diastereoselection.

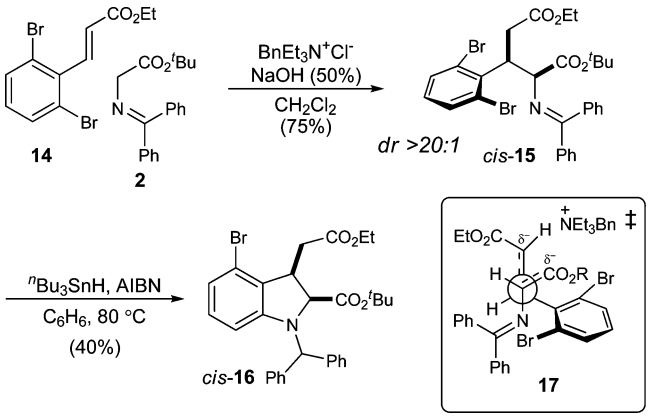
indoline ring can homolytically fragment at the carbon−nitrogen σ-bond. Following a thermodynamically driven σ-bond rotation, the carbon−nitrogen bond re-forms to give the *trans*-isomer. Rotation of one of the carbon−carbon bonds of the chain must occur, in addition to radical inversion, to reach the epimeric indoline radical intermediate.[28] This process is consistent with the observation that *cis*-indolines are more prone to isomerization than their *trans*-counterparts. It is significant to note that the isomerization can be prevented by several means, including the use of an electron-deficient benzophenone imine.[28] We were unable to locate the reduction product corresponding to **9**, consistent with our determination that ACCRI favors the ring isomer at equilibrium and that subsequent chain-terminating hydrogen atom transfer is reasonably fast relative to reduction of the equilibrium concentration of **9**.

Stereochemical Models for Diastereoselective Michael Additions. The diastereoselection observed in additions of glycine Schiff base **2** to unsaturated esters and nitriles was considerably higher (4:1) when using (*E*)-olefins **1b** relative to their (*Z*)-isomers.[30] We rationalize this using purely steric considerations and the two transition states outlined in Figure 2. The first assumption is the intermediacy of an (*E*)-enolate derived from the glycine Schiff base due to the steric bias of the large ammonium counterion. In the case of the (*E*)-isomer of the Michael adduct, the transition state **10** arising from attack of the enolate on the *Re* face leads to the *trans*-isomer in the product (*trans*-**6b**). This conformational arrangement suffers from nonbonded interactions involving both aryl and nitrile groups. Attack of the enolate on the *Si* face of the Michael acceptor leads to transition state **11**, eventually forming *cis*-**6b**. In this transition state, these nonbonded interactions are minimized and therefore would be lower in energy. This is reflected in the observed 87:13 ratio favoring the *cis*-isomer.

The lower selectivity (58:42 dr) observed for addition to (*Z*)-**1b** might be rationalized by the competition depicted in Figure 3. Addition of the enolate to the olefin *Re* face leads to transition-state assembly **12**. This transition state suffers from nonbonded interactions between the aryl group and the imine.

(30) Oare, D. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 157. Oare, D. A.; Heathcock, C. H. *Top. Stereochem.* **1989**, *20*, 87.

SCHEME 4



Similarly, *Si* face addition of the enolate would lead to transition state **13** in which nonbonded interactions exist among the cyano group, enolate oxygen, and quaternary ammonium counterion. Therefore, neither transition state would be preferred as they each suffer from torsional strain in the transition state, and this is reflected in the nearly 1:1 ratio of diastereomeric addition products formed.

If the interaction between the aromatic ring of the acceptor and azomethine (and its substituents) of the donor in **10** is a destabilizing influence as we postulate, then an increase in the effective size of the aromatic ring might lead to enhanced diastereoselection. We examined this possibility through the use of acceptor **14** (Scheme 4), as the *ortho*,*ortho*-disubstitution leads to a nonplanar styrene, and a corresponding increase in the steric destabilization in the transition state leads to the *trans*-adduct. Addition to **14** was indeed more diastereoselective, leading solely (>20:1) to *cis*-**15** in 75% yield. The putative transition state **17** describes how the *ortho*-substituents lead to a nonplanar acceptor and how its bromine substituents would be best accommodated away from the diphenylmethylene of the azomethine (cf. **10** and **11**). Cyclization of this intermediate to indoline *cis*-**16** proceeded well, but in moderate yield due to competitive product debromination.

Conclusion

In summary, two- and three-component couplings are described here that constitute strategically innovative approaches to the synthesis of 2,3-disubstituted indolines. Diastereoselection is maximized when *ortho*,*ortho*-disubstituted activated styrenes are employed in the Michael addition step. The multifunctional nature of the products is enhanced by their orthogonal protection (nitrile or ethyl ester vs *tert*-butyl ester, diphenylmethylamine). Incidentally, we have recently applied this annulation method to the preparation of the indole framework of ambiguine G.[31] Whereas the free radical-mediated aryl amination step is both efficient and easily manipulated, there remains a need for highly enantioselective direct additions of glycine Schiff base **2** to styrene-derived Michael acceptors.[17,32−34] Ultimately, the development of this type of enantioselective reaction in combination with the strategies disclosed here may directly advance the enantioselective construction of complex indoline alkaloids.

Experimental Section

***cis*/*trans*-2-(Benzhydrylideneamino)-3-(2-bromophenyl)-4,4-bis(ethoxycarbonyl)-6-methylhept-6-enoic Acid *tert*-Butyl Ester (*cis*/*trans*-7e).** A dichloromethane solution of alkylidene malonate **4a** (250 mg, 764 μmol), Schiff base 2 (225 mg, 764 μmol, 0.34 M), methallyl bromide (204 mg, 1.52 mmol), benzyltriethylammonium chloride (20 mol %), and 50% aq NaOH (20 equiv) was stirred rapidly at room temperature for 8 h. The mixture was diluted with ether, and the organic layer was washed with water and dried ($MgSO_4$). The residue obtained by filtration and concentration was then purified by flash chromatography (neutral alumina, 5% diethyl ether in hexanes) to afford the desired adducts as a separable 1:1 *cis*/*trans* mixture and colorless oil (486 mg, 95%): (*cis*-**7e**) R_f = 0.28 (20% EtOAc/hexanes); IR (film) 3062, 2978, 1732, 1625, 1190 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 8.3 Hz, 2H), 7.52 (dd, J = 8.0, 1.2 Hz, 1H), 7.42−7.39 (m, 3H), 7.35 (d, J = 7.6 Hz, 1H), 7.32−7.28 (m, 2H), 7.23−7.20 (m, 3H), 7.13 (td, J = 7.2, 1.0 Hz, 1H), 7.03 (td, J = 8.0, 1.6 Hz, 1H), 5.20 (d, J = 10.0 Hz, 1H), 4.74 (d, J = 10.0 Hz, 1H), 4.71 (s, 1H), 4.62 (s, 1H), 4.12−4.01 (m, 2H), 3.97−3.92 (m, 2H), 2.92 (d, J = 14.4 Hz, 1H), 2.45 (d, J = 14.4 Hz, 1H), 1.61 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H), 1.09 (t, J = 7.1 Hz, 3H), 0.97 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.0, 169.8, 169.2, 142.2, 140.1, 137.8, 136.8, 133.0, 131.0, 130.3, 129.2, 128.7, 128.4, 128.2, 127.8, 126.8, 114.3, 80.7, 68.8, 61.1, 60.9, 60.5, 53.8, 43.4, 27.4, 24.0, 13.9, 13.8; (*trans*-**7e**) R_f = 0.23 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, J = 8.0, 1.6 Hz, 1H), 7.59 (d, J = 7.1 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.41−7.39 (m, 3H), 7.36 (d, J = 8.0 Hz, 1H), 7.34−7.29 (m, 3H), 7.15−7.12 (m, 2H), 7.09 (td, J = 8.0, 1.6 Hz, 1H), 4.99 (d, J = 4.6 Hz, 1H), 4.70 (s, 1H), 4.62 (d, J = 4.6 Hz, 1H), 4.52 (s, 1H), 4.07−4.04 (m, 3H), 3.89−3.80 (m, 1H), 2.70 (d, J = 1.2 Hz, 2H), 1.59 (s, 3H), 1.22 (s, 9H), 1.15 (t, J = 7.1 Hz, 3H), 1.05 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 170.12, 170.08, 169.2, 142.1, 139.8, 137.2, 136.6, 133.5, 132.4, 130.4, 129.0, 128.9, 128.7, 128.6, 128.3, 128.03, 128.00, 126.6, 114.7, 81.5, 67.2, 61.3, 61.2, 60.6, 49.5, 42.4, 27.8, 23.6, 13.8; HRMS (EI) exact mass calcd for $C_{33}H_{33}{}^{79}BrNO_6$ [M − C_4H_9]$^+$, 618.1491, found 618.1464.

***trans*-2-(1-Benzhydryl-2-(*tert*-butoxycarbonyl)-2,3-dihydro-1*H*-indol-3-yl)-2-(2-methylallyl)malonic Acid Diethyl Ester (*trans*-5e).** A benzene solution of Michael adduct *trans*-**7e** (80 mg, 118 μmol), and ^{n}Bu$_3$SnH (144 μL, 534 μmol) in benzene (50 μM) was warmed to 85 °C. AIBN (23 mg, 142 μmol) was then added as a benzene solution by syringe pump over a 4−5 h period. The solution was refluxed for an additional hour, cooled, and concentrated. The residue was treated with a 1:1 (v/v) ether-satd aq KF solution and the resulting mixture stirred vigorously until a white precipitate formed. The organic layer was washed with water, dried ($MgSO_4$), filtered, and concentrated. The residue was then purified by flash chromatography (10% diethyl ether in hexanes) to furnish the indoline as a white solid (55 mg, 78%): mp 131.5−133.5 °C; R_f = 0.34 (20% EtOAc/hexanes); IR (film) 3062, 2978, 1732, 1602 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 7.7 Hz, 2H), 7.41 (d, J = 7.8 Hz, 2H), 7.29−7.27 (m, 3H), 7.23−7.19 (m, 3H), 7.13 (d, J = 7.3 Hz, 1H), 6.82 (t, J = 7.6 Hz, 1H), 6.57 (t, J = 7.5

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Hz, 1H), 5.90 (d, $J = 8.0$ Hz, 1H), 5.58 (s, 1H), 4.78 (s, 1H), 4.69 (s, 1H), 4.28 (d, $J = 2.2$ Hz, 1H), 4.19−4.07 (m, 3H), 4.00 (d, $J = 2.2$ Hz, 1H), 3.98−3.94 (m, 1H), 2.96 (d, $J = 14.4$ Hz, 1H), 2.70 (d, $J = 14.4$ Hz, 1H), 1.72 (s, 3H), 1.26 (s, 9H), 1.16 (t, $J = 7.2$ Hz, 3H), 0.93 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 170.4, 170.3, 151.1, 143.1, 141.8, 140.6, 129.7, 128.7, 128.6, 128.4, 127.9, 127.6, 127.3, 127.1, 126.3, 118.0, 115.2, 109.6, 81.2, 67.5, 67.3, 61.2, 61.1, 42.0, 27.9, 23.8, 14.0, 13.7; HRMS (EI) exact mass calculated for $C_{37}H_{43}{}^{79}BrNO_6$ $[M]^+$, 597.3090, found 597.3093. Anal. Calcd for $C_{37}H_{43}NO_6$: C, 74.35; H, 7.25; N, 2.34. Found: C, 74.39; H, 7.38; N, 2.25.

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Supporting Information Available: Experimental procedures and analytical data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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