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Rhodium-Catalyzed Direct C−H Addition of 3,4-Dihydroquinazolines to Alkenes and Their Use in the Total Synthesis of Vasicoline

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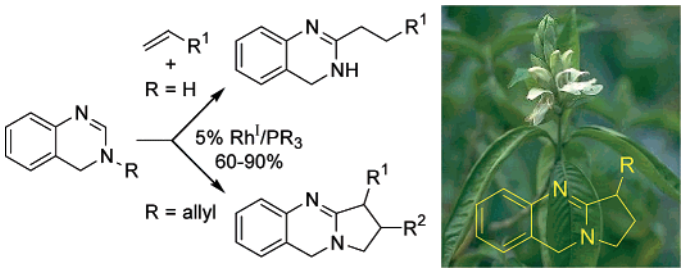

The inter- and intramolecular couplings of unactivated alkenes to 3,4-dihydroquinazolines with a Rh(I) catalyst are reported. Coupling between olefins and *NH*-3,4-dihydroquinazoline was found to occur consecutively with heterocycle dehydrogenation in the presence of a Rh(I)/PCy_3/HCl catalyst. The reaction was used to develop an effective method for the synthesis of 2-substituted quinazolines through an oxidative workup step. The regiocontrolled synthesis and Rh-catalyzed cyclization of alkene-tethered 3,4-dihydroquinazolines are also described. Applying this method, the second total synthesis of vasicoline was achieved. The key Rh-catalyzed cyclization step was made possible by the use of a rigid bicyclic phosphine ligand. The synthesis further demonstrates a challenging Cu-catalyzed amidation of an ortho-substituted aryl chloride.

Introduction

Metal-catalyzed C−H activation[1] has recently emerged as a powerful tool for heterocycle functionalization.[2] Our group and others have shown that the C−H activation of *N*-heterocycles can be used to achieve coupling to aryl halides[3] and addition across C−C π-bonds.[4] The regioselectivity of heterocycle C−H transformations is generally a result of either (1) the preference of electrophilic catalysts for a substrate's most nucleophilic position or (2) the complex-induced ortho-directing effect of a ring-heteroatom. Our group has exploited the latter mechanism to achieve selective coupling of olefins and aryl iodides to the 2-position of aromatic azoles (Scheme 1).[5,6] These reactions are believed to proceed via a catalyst−substrate complex wherein

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(1) (a) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211. (b) Jun, C. H.; Lee, J. H. *Pure Appl. Chem.* **2004**, *76*, 577. (c) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731.

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(5) For a summary of this work see: Wiedemann, S. H.; Bergman, R. G.; Ellman, J. A. In *Handbook of C−H Transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, Germany, 2005; Vol. 1, p 187.

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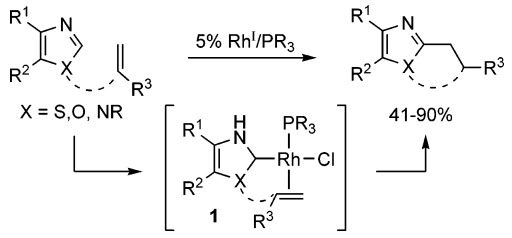
SCHEME 1



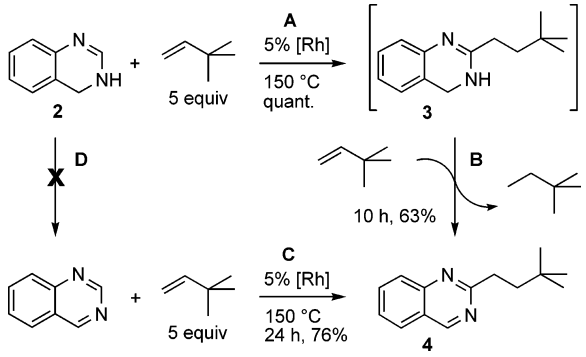
the azole is bound to rhodium as an *N*-heterocyclic carbene (NHC) ligand (**1**).[3d,7,8] Just as NHC ligands with either saturated or aromatic backbones have similar properties,[9] we were able to show that saturated azolines react similarly to aromatic azoles in the presence of a Rh(I) catalyst.[10] For example, 4,4-dimethyloxazoline can be effectively coupled to unactivated olefins under mild conditions to give products useful as protected carboxylic acids.[4f]

These findings suggest that other heterocycles capable of forming and stabilizing an NHC tautomer might also be viable substrates for C−H addition to olefins. The quinazoline skeleton, in its various oxidation states, is a common structural motif in compounds that have been isolated and synthesized by medicinal chemists since the 19th century.[11] We now wish to report a new entry into this compound class via the C−H addition of 3,4-dihydroquinazolines (DHQs) to olefins. From the inter- and intramolecular coupling reactions disclosed herein, medicinally relevant molecular architecture can be assembled. One application to the total synthesis of vasicoline is described in detail.

Results and Discussion

Intermolecular Coupling. Parent 3,4-dihydroquinazoline (**2**) is a convenient heterocycle synthon because it can be prepared in one step from commercial starting materials, and it resists oxidation during prolonged benchtop storage.[12] We have previously reported that **2** can be phenylated at C-2 by iodobenzene in the presence of a Rh(I) catalyst derived from $[RhCl(coe)_2]_2$ and PCy_3 (coe = *cis*-cyclooctene, Cy = cyclohexyl).[3d] This reaction occurs under conditions identical with those used for the arylation of azoles, providing evidence for a common reaction mechanism. As in the arylation reaction, previously published conditions for the C−H coupling of azoles to olefins[4e] led to the selective alkylation of **2** at the C-2 position (Scheme 2). Unlike the reactions of azoles, however, in the coupling reaction of **2** with excess 3,3-dimethylbutene a significant byproduct, aromatized 2-(3,3-dimethylbutyl)-3,4-dihydroquinazoline (**4**, reaction B), was formed in addition to the expected product, 2-(3,3-dimethylbutyl)quinazoline (**3**, reaction A).

SCHEME 2. Rh-Catalyzed Domino C−H Addition/Dehydrogenation[a]



[a] 5% [Rh] = 2.5 mol % of $[RhCl(coe)_2]_2$, 4 mol % of PCy_3·2HCl, 2.5 mol % of PCy_3, THF.

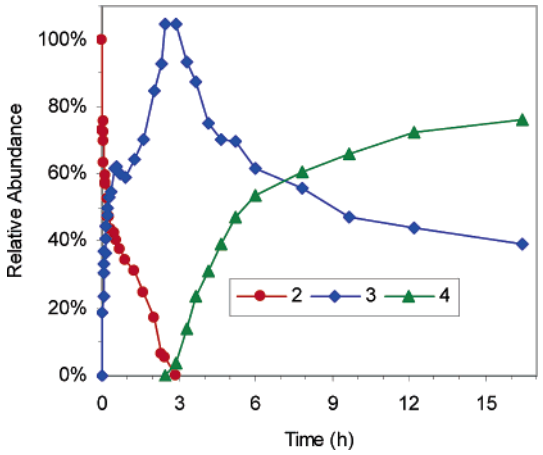


FIGURE 1. Coupling and oxidation of **2** monitored by in situ ^1H NMR analysis.

Given that Rh(I)/PCy_3 is a competent catalyst for the transfer dehydrogenation of alkanes,[13] we reasoned that **4** could arise from formal H_2 transfer from **3** to 3,3-dimethylbutene. Other possibilities include an uncatalyzed dehydrogenation[14] of **3** or initial dehydrogenation of **2** followed by Rh-catalyzed alkylation. While this latter pathway seems likely given that quinazoline does indeed couple directly with 3,3-dimethylbutene (reaction C), both alternative mechanisms were ruled out by in situ ^1H NMR analysis (Figure 1).[15] During the reaction of **2** with 3,3-dimethylbutene, quinazoline does not form (reaction D), and its transient formation along the path to **4** was ruled out because, in isolated form, quinazoline alkylates more slowly than **2**.

(6) For a thorough study of the C−H activation mechanism operative in these reactions see: Wiedemann, S. H.; Lewis, J. C.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* Accepted for publication.

(7) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 3202.

(8) Cavell and co-workers have disclosed a related, but mechanistically distinct C−H addition reaction of imidazolium salts to olefins.[4c] A Ni−NHC complex analogous to their proposed catalytic intermediates has been isolated: Clement, N. D.; Cavell, K. J.; Jones, C.; Elsevier, C. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1277.

(9) (a) Hillier, A. C.; Sommer, W. J.; Yong, B. S.; Petersen, J. L.; Cavallo, L.; Nolan, S. P. *Organometallics* **2003**, *22*, 4322. (b) Lee, M.-T.; Hu, C.-H. *Organometallics* **2004**, *23*, 976.

(10) For a detailed computational study showing insignificant differences between the oxidative addition reactions of 1,3-dimethylimidazolium and 1,3-dimethyl-4,5-dihydroimidazolium with $(PR_3)_xRhCl$, see: Hawkes, K. J.; McGuinness, D. S.; Cavell, K. J.; Yates, B. F. *Dalton Trans.* **2004**, 2505.

(11) Studies of these alkaloids have been reviewed comprehensively[11a] and continue to be reviewed annually.[11b] (a) Johne, S. In *The 2nd supplements to the 2nd edition of Rodd's Chemistry of Carbon Compounds*; Sainsbury, M., Ed.; Elsevier: Amsterdam, The Netherlands, 2000; Vol. IV I/J, pp 203−231. (b) Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 650.

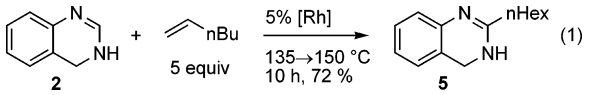
(12) We reported this new synthesis of **2** (ref 3d) based on a previous 2-step synthesis: Burdick, B. A.; Benkovic, P. A.; Benkovic, S. J. *J. Am. Chem. Soc.* **1977**, *99*, 5716−5725.

(13) (a) Wang, K.; Goldman, M. E.; Emge, T. J.; Goldman, A. S. *J. Organomet. Chem.* **1996**, *518*, 55. (b) Itagaki, H.; Murayama, H.; Saito, Y. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1254.

(14) Spontaneous dehydrogenation of 1,2,3,4-tetrahydroquinazolines has been described: Telezhenetskaya, M. V.; Plugar, V. N. *Khim. Prir. Soedin.* **1991**, *27*, 149. Telezhenetskaya, M. V.; Plugar, V. N. *Chem. Nat. Compd.* **1991**, *27*, 133.

(15) The unusual profile observed for the conversion of **2** to **3** cannot be fully explained at this time.

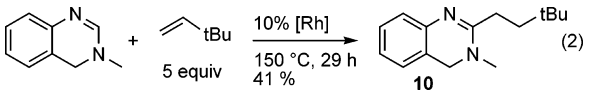
Interestingly, complete conversion of **2** to **3** occurs before any **4** is formed. This result is consistent with the idea that heterocycles function both as ligands and as substrates during the olefin coupling reaction. After all DHQ (**2**) has been consumed, the catalyst changes its ligand set and is transformed from a selective C−H coupling catalyst to one that is competent for transfer hydrogenation.[16] With prolonged heating it is possible to isolate **4** as the major product of the reaction (Scheme 2, reactions A and B). Alternatively, with careful reaction monitoring, the synthetically useful DHQ product can also be isolated in good yield (eq 1). DHQs can be readily converted



to the corresponding quinazolines,[17] quinazolinones,[18] or 1,2,3,4-tertrahydroquinazolines.[19]

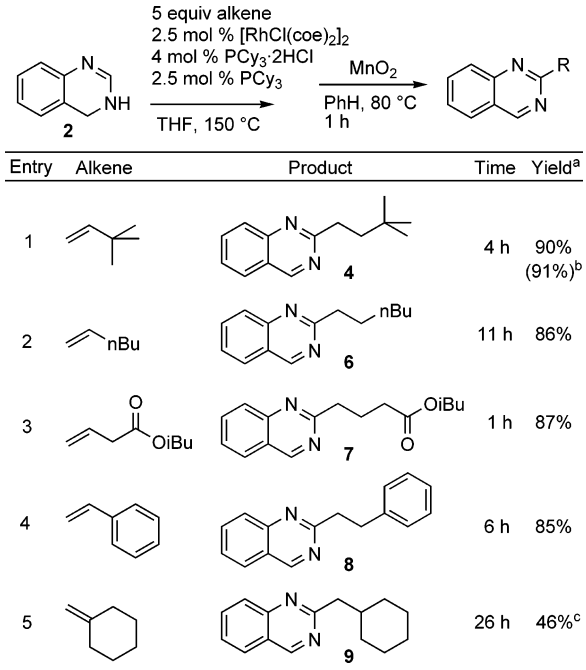
Despite the moderate yields obtained upon isolation of either **4** or **5**, reaction monitoring by in situ ^{1}H NMR analysis revealed that the coupling of **2** to a variety of monosubstituted olefins proceeds quantitatively. We therefore sought a convenient workup protocol that would provide isolated products in yields more reflective of true coupling efficiency. The best results were obtained by oxidizing crude coupling reaction mixtures with MnO_2.[17] Because MnO_2 oxidation converts 2-substituted DHQs to quinazolines, just as Rh(I)/PR$_3$ does, careful monitoring of reaction progress is not necessary with this protocol; the reactions can be terminated anytime after the first equivalent of olefin is consumed without affecting the yield of isolated quinazoline products.

The reaction between various olefins and **2** catalyzed by $[RhCl(coe)_2]_2$, PCy_3, and an acid additive[20] afforded 2-alkylated quinazolines in high yield after oxidative workup with MnO_2 (Table 1).[21] Even olefins susceptible to Rh(I)-catalyzed double-bond isomerization underwent selective C−C bond formation at the alkene terminal position (entries 2 and 3). In contrast to previously reported M−NHC mediated couplings involving styrene,[4e,f] **2** was also coupled to styrene in high yield (entry 4). Lower yields were obtained when either the olefin (entry 5) or the heterocycle (eq 2) was more highly substituted.[22]



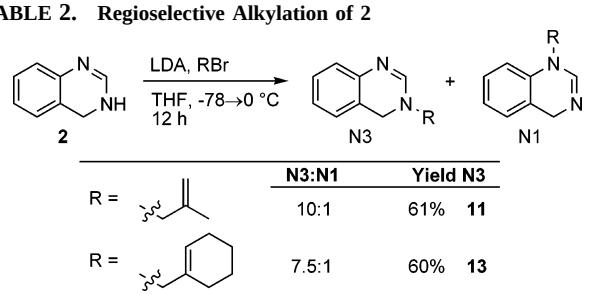
Intramolecular Coupling. The intramolecular version of DHQ/olefin coupling can be used to form ring-fused pyrrolo-[2,1-*b*]quinazolines, a common scaffold in medically relevant natural products. While *N*-alkylation of **2** provides the most direct access to alkene-tethered DHQ cyclization substrates,[23] no methods for discriminating between the two nucleophilic sites (N1 and N3) of **2** have been disclosed.[24] As resonance arguments would predict, we found that direct alkylation reactions of **2** run under a variety of conditions afforded regioisomeric mixtures favoring the conjugated amidine (N3) product. The combination of polar solvents and low temperatures led to useful regioselectivities (Table 2).[25] When 3-allyl-DHQs were treated with our typical catalyst mixture derived from $[RhCl(coe)_2]_2$ and PCy_3·2HCl[26] the expected cyclized products were obtained in good yields (Table 3).[27] The reaction was effectively applied to a highly substituted olefin (**13**), selectively affording the expected cis-fused tetracyclic product. A 1,4-dihydroquinazoline (**15**), the minor regioisomer of DHQ alkylation, also underwent cyclization, albeit with reduced efficiency and selectivity.

TABLE 1. Rh-Catalyzed Intermolecular C−H Coupling of 2 to Olefins



[a] Two steps. [b] Coupling carried out at 135 °C. [c] Quantities of all catalyst components were doubled.

TABLE 2. Regioselective Alkylation of 2



(16) The product of transfer hydrogenation, 2,2-dimethylbutane, was also detected at levels commensurate with **4** formation.

(17) Kreher, R.; Bergmann, U. *Heterocycles* **1981**, *16*, 1693.

(18) Mehta, D. R.; Naravane, J. S.; Desai, R. M. *J. Org. Chem.* **1963**, *28*, 445.

(19) Zharekeev, B. K.; Telezhenetskaya, M. V.; Khashimov, K. N.; Yunusov, S. Y. *Khim. Prir. Soedin.* **1974**, *10*, 679. Zharekeev, B. K.; Telezhenetskaya, M. V.; Khashimov, K. N.; Yunusov, S. Y. *Chem. Nat. Compd.* **1974**, *10*, 704.

(20) The role of the acid additive in accelerating catalysis has not yet been ascertained.

(21) Excess amounts of olefin (5 equiv with respect to heterocycle) were used for this work. In previous studies of related reactions, the use of less than 5 equiv of the olefin component led to significant reductions in reaction rate[4e] and yield.[4f]

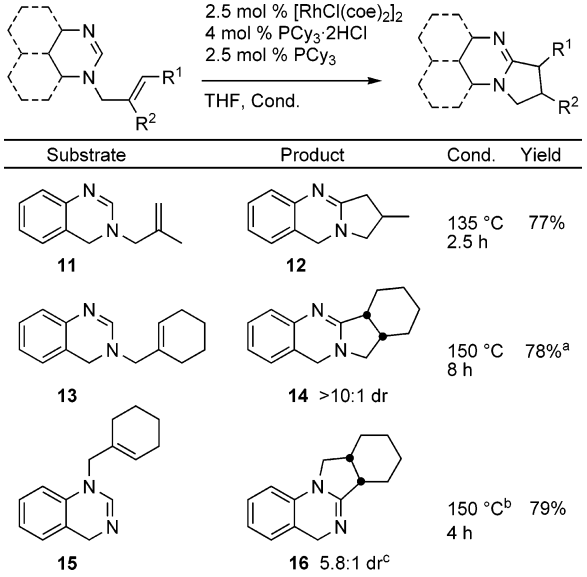
(22) In previous studies of related reactions, the coupling of the 1,2-disubstituted olefin cyclohexene was either ineffective[4i] or only mildly effective[4f] compared to coupling reactions of less substituted olefins.

(23) An elegant, but less convergent method for preparing *N*3-substituted DHQs involves selective alkylation of *o*-aminobenzylamine, using 9-BBN as a protecting and directing group: Bar-Haim, G.; Kol, M. *Tetrahedron Lett.* **1998**, *39*, 2643.

(24) The sole report of nucleophilic alkylation of **2** (with iodomethane) claims exclusive *N*3-selectivity. We were unable to reproduce this result: Armarego, W. L. *J. Chem. Soc.* **1961**, 2697.

(25) Isomeric mixtures were separated by chromatography.

TABLE 3. Rh-Catalyzed Intramolecular Olefin Coupling of Allyldihydroquinazolines



[a] Single isomer. [b] Quantities of all catalyst components were doubled. [c] Not separated.

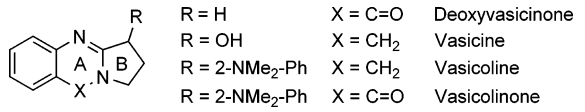
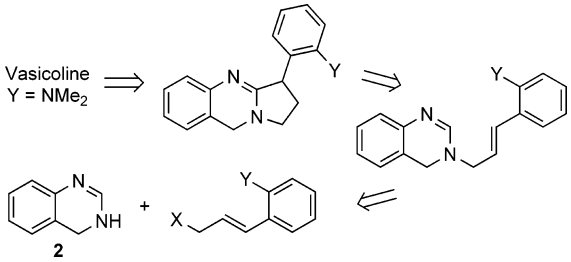


FIGURE 2. Common alkaloids isolated from *Adhatoda vasica*.

Total Synthesis of Vasicoline. Quinazoline natural products isolated from plant and microbial sources have been studied for antimalarial,[28] antiinflamatory,[29] and antitumor[30] activity. Several medicinal herbs of south Asia, such as *Adhatoda vasica*,[31] have quinazoline alkaloids as their active constituents (Figure 2). To demonstrate the utility of our Rh-catalyzed DHQ/olefin coupling in the preparation of medicinally relevant natural products, we undertook a total synthesis of one of these structures, vasicoline.[32]

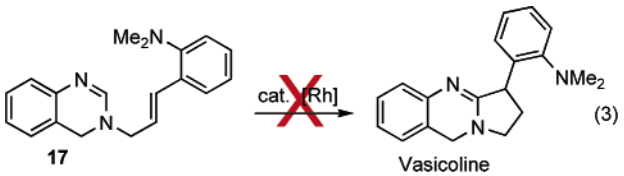
Like other quinazoline natural products, vasicoline is typically isolated together with its 4-oxidized (pyrrolo[2,1-*b*]quinazolinone) analogue, vasicolinone.[33] Several general strategies for the synthesis of pyrrolo[2,1-*b*]quinazolinones have been developed, including the intramolecular aza-Wittig reaction,[34] lactam condensations with isatoic anhydride,[35] and microwave-promoted cyclodehydrations.[36] In contrast, little attention has been devoted to the synthesis of the more reduced, and significantly less stable class of alkaloids, the 1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolines, of which vasicoline is a member.[37]

SCHEME 3. General Strategy for the Total Synthesis of Vasicoline



Vasicoline has been synthesized only once previously by Stevens and Nakagawa.[38] Their approach relied on the moderately selective bis-ortho-nitration of 1-benzyl-3-phenylpyrrolid-2-one by $AcONO_2$. We envisaged forming the B-ring of vasicoline via the Rh-catalyzed intramolecular olefin coupling of a suitably functionalized 3-cinnamyl-DHQ (Scheme 3). The cyclization substrate could be prepared by cinnamylation of **2** with an appropriate alkylating agent.

o-Dimethylaminocimmanyl-3,4-dihydroquinazoline (**17**) was chosen as an initial synthetic target because its cyclization would directly provide vasicoline. Unfortunately, under all reaction conditions investigated, **17** reacted stoichiometrically, rather than catalytically, with Rh(I)/PCy_3 to give an uncharacterized product (eq 3). Considering the proximity of the basic dimethyl aniline



moiety of **17** to the site of desired C−C bond formation, catalyst entrapment may be involved in preventing turnover. We therefore elected to install the aniline nitrogen atom of vasicoline at a late stage by metal-catalyzed aryl-chloride amination.[39] If catalyst inactivation by **17** were caused by its ortho substituent,

(26) We only recently recognized that the treatment of PCy_3 with HCl in ether at 25 °C can produce both PCy_3·2HCl and PCy_3·HCl. These two salts perform identically in the applications for which we use them. They can be independently prepared by using controlled stoichiometry (see Experimental Section). PCy_3·2HCl is quite hygroscopic and exhibits unusual spectroscopic properties, especially in the infrared band, on account of its triple ion, Cl−H−Cl$^-$ (bent). For a previous synthesis of phosphonium dihalohydrogenate salts with neat hydrogen halides at low temperatures see: Kohle, R.; Kuchen, W.; Peters, W. *Z. Anorg. Allg. Chem.* **1987**, *551*, 179.

(27) Interestingly, **12** has been previously synthesized by rhodium-catalyzed annulation. It was isolated as a byproduct in 20−30% from the syngas hydroformylation of 2-[(2-methylallylamino)methyl]phenylamine catalyzed by $[Rh(OAc)_2]_2$/PPh_3: Campi, E. M.; Habsuda, J.; Jackson, W. R.; Jonasson, C. A. M.; McCubbin, Q. J. *Aust. J. Chem.* **1995**, *48*, 2023.

(28) Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H. *Tetrahedron Lett.* **1999**, *40*, 2175.

(29) Al-Shamma, A.; Drake, S.; Flynn, D. L.; Mitscher, L. A.; Park, Y. H.; Rao, G. S. R.; Simpson, A.; Swayze, J. K.; Veysoglu, T.; Wu, S. T.-S. *J. Nat. Prod.* **1981**, *44*, 745.

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(32) Johne, S.; Groger, D.; Hesse, M. *Helv. Chim. Acta* **1971**, *54*, 826.

(33) Vasicolinone has also been twice synthesized in tandem with rutaecarpine, another structurally homologous quinazolinone alkaloid: (a) Kaneko, C.; Chiba, T.; Kasai, K.; Miwa, C. *Heterocycles* **1985**, *23*, 1385. (b) Kokosi, J.; Szasz, G.; Hermecz, I. *Tetrahedron Lett.* **1992**, *33*, 2995.

(34) (a) Takeuchi, H.; Hagiwara, S.; Eguchi, S. *Tetrahedron* **1989**, *45*, 6375. (b) Eguchi, S.; Suzuki, T.; Okawa, T.; Matsushita, Y.; Yashima, E.; Okamoto, Y. *J. Org. Chem.* **1996**, *61*, 7316.

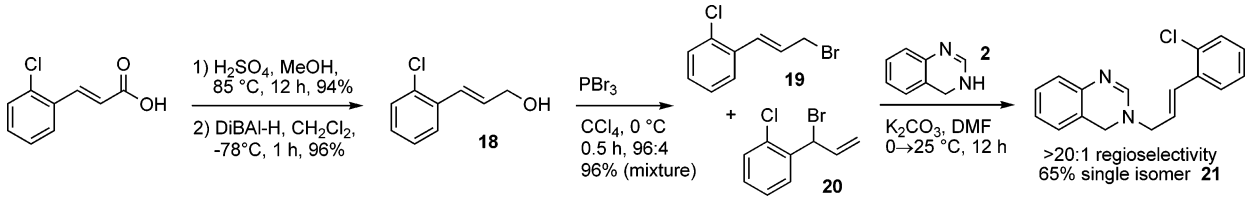
(35) Yadav, J. S.; Reddy, B. V. S. *Tetrahedron Lett.* **2002**, *43*, 1905.

(36) Liu, J. F.; Ye, P.; Sprague, K.; Sargent, K.; Yohannes, D.; Baldino, C. M.; Wilson, C. J.; Ng, S. C. *Org. Lett.* **2005**, *7*, 3363.

(37) Zn^0/acetic acid reduction of quinazolinones[37a] and tandem nitroarene reduction/condensation strategies[37b,c] have been used for the synthesis of 1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolines: (a) Karimov, A.; Telezhenetskaya, M. V.; Yunusov, S. Y. *Khim. Prir. Soedin.* **1982**, *18*, 498. Karimov, A.; Telezhenetskaya, M. V.; Yunusov, S. Y. *Chem. Nat. Compd.* **1982**, *18*, 466. (b) Southwick, P. L.; Cremer, S. E. *J. Org. Chem.* **1959**, *24*, 753. (c) Downes, A. M.; Lions, F. *J. Am. Chem. Soc.* **1950**, *72*, 3053.

(38) Nakagawa, Y.; Stevens, R. V. *J. Org. Chem.* **1988**, *53*, 1873.

SCHEME 4



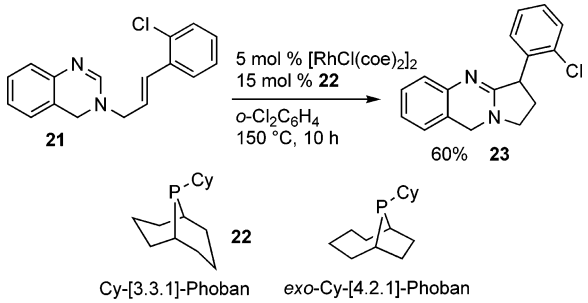
then presumably cyclization in the presence of a less basic ortho substituent (e.g. chloride) would be more favorable.

Preparation of a suitable chlorinated cyclization substrate began from commercially available *o*-chlorocinnamic acid (Scheme 4). Esterification followed by hydride reduction afforded *o*-chlorocinnamyl alcohol (**18**) in high yield over two steps.[40] Treatment of **18** with PBr_3 gave the corresponding cinnamyl bromide **19** in high yield, accompanied by minor amounts of conjugate bromination product **20**.[41] When **2** was treated with either pure **19** or a mixture of **19** and **20** in DMF, cyclization precursor **21** was isolated in good yield after separation of regioisomers.

We expected **21** to be a challenging substrate for Rh-catalyzed C−H coupling because similar cinnamyl-substituted heterocycles have cyclized in moderate yield[4g] and **21**, in particular, has the potential to undergo side reactions arising from Rh-mediated cleavage of its Ar−Cl bond. Indeed, the conditions optimized for the cyclization of other *N*-allyl-3,4-DHQs ([RhCl(coe)$_2$]$_2$/PCy$_3$/HCl) provided low turnover and substantial substrate decomposition when applied to **21**. Omitting the acid additive reduced the amount of undesired de-cinnamylation products observed. Still, catalyst activity and lifetime were too low to be synthetically useful.

At this time we became aware of a report describing the use of conformationally rigid cyclohexyl-Phoban ligands as replacements for PCy_3.[42] Ruthenium alkylidene catalysts derived from these ligands exhibit enhanced stability and selectivity for the self-metathesis of olefins. When **21** was treated with a mixture of [RhCl(coe)$_2$]$_2$ and one of these ligands (Cy-[3.3.1]-Phoban,[43] **22**), in *o*-dichlorobenzene, cyclized product **23** was isolated in good yield (Scheme 5). Alternatively, the catalyst mixture derived from a more readily available ∼2:1 mixture of Cy-[3.3.1]-Phoban and *exo*-Cy-[4.2.1]-Phoban isomers could be used without reduction in yield.[44] Phoban ligands have also proven to be superior replacements for PCy_3 in a related Rh(I)-catalyzed C−H activation/arylation of azoles,[3a] presumably because they exhibit the steric and electronic properties of bulky tri-secondary-alkylphosphines while being less susceptible to cyclometalation-type decomposition.[45]

SCHEME 5



Once the carbon framework of vasicoline was in place, we confronted the challenge of aminating **23**. Metal-catalyzed substitution of an aryl chloride by $HNMe_2$ has not been previously disclosed, nor did this reaction proceed in our hands in the presence of various catalysts. In comparison, the metal-catalyzed substitution of aryl chlorides with ammonia equivalents has been extensively studied. The substitution of **23** with an ammonia equivalent to give didesmethylvasicoline (**24**) was especially attractive to us because **24** is the penultimate intermediate of Stevens's vasicoline synthesis. To complete the formal synthesis of vasicoline we considered a number of aryl halide amination methods, employing a variety of ammonia equivalents. Various properties of **23**—a relatively unreactive leaving group (Cl),[46] steric hindrance at the position ortho to the leaving group, and a relatively acidic position α to the amidine—rendered it a particularly challenging amination substrate.

Having quickly eliminated Pd-catalyzed carbamate couplings because they exhibit low reactivity toward aryl chlorides,[47] and catalytic amination methods relying on M[HMDS]$_x$,[48] for similar reasons,[49] benzophenone imine emerged as the most appropriate ammonia synthon for our purposes. It is not sterically demanding, its N−H bond is quite reactive, and it has been shown to operate in conjunction with mild heterogeneous bases (e.g., K_3PO_4 and $CsCO_3$).[50] Despite that, slow hydrodechlorination was observed as the only reaction between **23** and benzophenone

(39) We also considered altering our synthetic route by exchanging the dimethylamino group for an *N*-protected amino group. These efforts led to lengthy reaction sequences.

(40) This two-step sequence was preferred to direct reduction of *o*-chlorocinnamic acid because common procedures for carboxylic acid reduction gave competitive conjugate reduction.

(41) Isomerically pure **19** can be obtained by using milder bromination conditions (e.g., $CHBr_3$/PPh_3); however, the PBr_3 method is more amenable to use on large scale.

(42) Forman, G. S.; McConnell, A. E.; Hanton, M. J.; Slawin, A. M. Z.; Tooze, R. P.; van Rensburg, W. J.; Meyer, W. H.; Dwyer, C.; Kirk, M. M.; Serfontein, D. W. *Organometallics* **2004**, *23*, 4824.

(43) Cy-[3.3.1]-Phoban was prepared in moderate yield by alkylation of H-[3.3.1]-Phoban with BuLi/CyBr: (a) Meyer, W. H. Personal communication. (b) Dwyer, C. L.; Kirk, M. M.; Meyer, W. H.; van Rensburg, W. J.; Forman, G. S. *Organometallics*. Submitted for publication (om051079p).

(44) Available from radical initiated coupling of $CyPH_2$ with 1,5-cyclooctadiene (see ref 42).

(45) Hietkamp, S.; Stufkens, D. J.; Vrieze, K. J. *Organomet. Chem.* **1978**, *152*, 347.

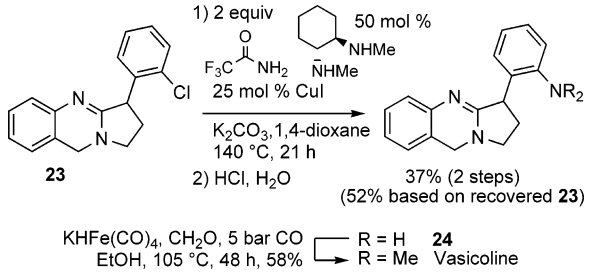
(46) A synthesis of the −Br analogue of **23** was undertaken starting from 2-bromocinnamic acid. The method used to prepare **23** proved ineffective in this effort; the Rh-catalyzed cyclization step produced an uncharacterized mixture of decomposition products.

(47) Ar−Cl/carbamate couplings employing Pd/P*t*Bu$_3$[47a] and Pd/Xantphos[47b] have been reported: (a) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575. (b) Yin, J. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043.

(48) Ar−Cl/M[HMDS]$_x$ couplings employing M = Li[48a] and Zn[48b] have been reported: (a) Lee, S.; Jorgensen, M.; Hartwig, J. F. *Org. Lett.* **2001**, *3*, 2729. (b) Lee, D. Y.; Hartwig, J. F. *Org. Lett.* **2005**, *7*, 1169.

(49) Ortho-Substituted aryl chlorides, normally inactive under Pd/LiHMDS coupling conditions,[48a] were shown to be effectively aminated in the presence of a sterically minimal ammonia shuttle, Ph_3SiNH_2. Unfortunately, these reaction conditions did not function for **23**, probably due to its base sensitivity: Huang, X. H.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3417.

SCHEME 6



imine in the presence of $Pd_2(dba)_3$ and Buchwald's biaryl ligand, 2-(dicyclohexylphosphino)-2′-(*N*,*N*-dimethylamino)biphenyl.

Broadening our search of amination methods to include less conventional approaches, we next considered amide couplings for the preparation of **24**. Amides are not typically used as ammonia synthons because extreme pH values and temperatures are required to cleave amide bonds. Nevertheless, based on Stevens's use of refluxing HCl as part of a workup procedure for the synthesis of **24**, we were encouraged to consider amide coupling/amide hydrolysis for the amination of **23**. Pd-catalyzed amide-coupling conditions proved unreactive toward **23**,[47b] even in the presence of Keay's potent BINAP−Fu ligand.[51] Successful C−N bond formation was finally achieved with Buchwald's Cu-catalyzed Goldberg-type amidation method (Scheme 6).[52] At elevated temperatures, various aryl and alkyl primary amides were coupled to **23** in fair yield by a CuI/diamine catalyst mixture. Trifluoroacetamide was found to give the highest yield (based on recovered starting material) of aminated product **24** after hydrolytic workup. Changes to catalyst loading, reaction temperature, and other conditions did not improve conversion without leading to increased substrate decomposition as well.

The final step in Stevens' and our synthesis of vasicoline was the dimethylation of **24**. Typical nucleophilic conditions for this type of transformation were not usable because the amidine functionality of **24** is more nucleophilic than the NH_2 group. Methylation of the anilide anion of **24** was also ineffective because of competing amidine−enolate formation. Stevens reported quantitative formation of vasicoline by reductive amination of formaldehyde with $KHFe(CO)_4$ under CO atmosphere.[53] This very mild reductant was called for because more typical $NaCNBH_3$-mediated reductive amination conditions led to undesired amidine reduction.[54] Although in our hands Stevens's published procedure for $KHFe(CO)_4$ reduction did not lead to high conversion of starting material, by increasing temperature, pressure, and reagent concentrations we did obtain vasicoline in 58% yield (Scheme 6). Our synthesis of vasicoline proceeds in 7 linear steps from commercial materials with 10% overall yield—an efficiency identical with that reported for the Stevens synthesis.

Conclusion

In summary, we have (1) demonstrated that 3,4-dihydroquinazolines effectively participate in Rh-catalyzed C−H/olefin coupling both inter- and intramolecularly, (2) identified an interesting instance of controlled domino catalysis involving a Rh-catalyzed dehydrogenation, and (3) utilized DHQ/olefin couplings to provide access to medicinally relevant substituted quinazolines and ring-fused dihydroquinazolines via an unusual bond disconnection. Using Rh-catalyzed C−H activation/olefin insertion we went on to achieve the second total synthesis of vasicoline. In the course of our synthesis we demonstrated that rigid bicyclic trialkylphosphines can function as potent alternatives to PCy_3 in C−H activation reactions. Finally, we reported moderately effective conditions for a particularly challenging aryl chloride amination using, for the first time, trifluoroacetamide as an ammonia synthon.

Experimental Section

General Procedure for the Coupling/Oxidation of 2 with Olefins. In a N_2 atmosphere glovebox **2** (132 mg, 1.00 mmol), $[RhCl(coe)_2]_2$ (18 mg, 0.025 mmol), olefin (5 mmol), PCy_3·2HCl (16 mg, 0.045 mmol), and PCy_3 (7 mg, 0.025 mmol) were combined in 10 mL of a mixture of THF and d_8-THF (20:1). An aliquot of this solution (0.5 mL) was flame sealed under vacuum into a medium-walled NMR tube. The remainder of the reaction solution was sealed into a glass-walled vessel equipped with a vacuum stopcock and both reaction tubes were heated to 150 °C in an oil bath. Periodically, the NMR tube was removed from the heating bath then cooled to room temperature, and a one-pulse ^1H NMR spectrum was acquired. Once ^1H NMR indicated complete consumption of **2**, both reaction vessels were cooled to 25 °C and their contents transferred to a round-bottom flask with 40 mL of benzene. MnO_2 (1.4 g, 16 mmol) was added to this reaction solution and then it was heated to reflux for 1 h. While the reaction suspension was still hot, it was vacuum filtered through Celite. The filter plug was further rinsed with benzene (25 °C, 10 mL). The filtrate was concentrated under vacuum and then purified by column chromatography.

General Procedure for the Preparation of 3-Substituted DHQs. In a round-bottom flask under N_2 **2** (132 mg, 1.00 mmol) and alkylating agent (1.10 mmol) were combined in THF (10 mL). The reaction solution was cooled to −78 °C and a solution of lithium diisopropylamide (118 mg, 1.10 mmol) in THF (1 mL) was added dropwise. After 2 h the reaction solution was warmed to 25 °C and stirred overnight. Analysis of the crude reaction mixture by ^1H NMR analysis was used to determine regioselectivity between 3,4-dihydro- and 1,4-dihydroquinazoline products. The crude reaction mixture was concentrated under vacuum onto a small amount of silica. Column chromatography was used to separate and purify regioisomers.

General Procedure for Intramolecular Olefin Coupling Reactions of DHQs. In a N_2 atmosphere glovebox olefin-tethered DHQ (1.00 mmol), $[RhCl(coe)_2]_2$ (18 mg, 0.025 mmol), PCy_3·2HCl (16 mg, 0.045 mmol), and PCy_3 (7.0 mg, 0.025 mmol) were combined in 10 mL of a mixture of THF and THF-d_8 (20:1). An aliquot of this solution (0.5 mL) was flame sealed under vacuum into a medium-walled NMR tube. The remainder of the reaction solution was sealed into a glass-walled vessel equipped with a vacuum stopcock and both reaction tubes were heated in an oil bath. Periodically, the NMR tube was removed from the heating bath then cooled to room temperature, and a one-pulse ^1H NMR spectrum was acquired. After ^1H NMR analysis indicated that olefin had been completely consumed. Both reaction vessels were then cooled to 25 °C and their contents concentrated under vacuum onto a small amount of silica. Reaction products were purified by column chromatography.

(50) (a) Grasa, G. A.; Viciu, M. S.; Huang, J. K.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729. (b) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J. J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158. (c) Stauffer, S. R.; Lee, S. W.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423.

(51) Andersen, N. G.; Parvez, M.; McDonald, R.; Keay, B. A. *Can. J. Chem.* **2004**, *82*, 145.

(52) (a) Klapars, A.; Huang, X. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421. (b) Klapars, A.; Antilla, J. C.; Huang, X. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (c) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453.

(53) Watanabe, Y.; Shim, S. C.; Mitsudo, T.; Yamashita, M.; Takegami, Y. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1378.

(54) We noted equally unselective reduction of **24** when milder $NaHB(OAc)_3$ or Eschweiler−Clarke conditions were used.

Tricyclohexylphosphonium Hydrogen Dichloride (PCy_3·2HCl). The reaction was carried out according to a modified literature procedure that was believed to provide PCy_3·HCl.[4g] In a round-bottom flask under N_2, PCy_3 (1.08 g, 3.85 mmol) was dissolved in diethyl ether (25 mL). A solution of HCl (1 N in ether, 7.1 mL) was added dropwise with stirring. After 20 min the white precipitate was filtered under N_2 through a glass frit, washed with ether (2 × 10 mL), and dried under vacuum over P_2O_5. The resulting white powder (1.12 g, 82%) was stored under N_2. IR (Figure S-2f, Supporting Information): 2933, 2853, 2393 (P−H), 1451, 765 (vbr, vs, Cl−H−Cl) cm^{-1}. ^1H NMR: δ 7.59 (br s, 1H, Cl*H*Cl), 7.22 (br d, 1H, J_{P-H} = 482 Hz, P*H*), 2.54 (m, 3H, PC*H*), 2.2−1.2 (m, 30H). ^{13}C NMR (100 MHz): δ 28.4 (d, J_{P-C} = 39.3 Hz), 27.9 (d, J_{P-C} = 3.4 Hz), 26.3 (d, J_{P-C} = 12.6), 25.1. ^{31}P NMR (160 MHz): δ 23.0. Anal. Calcd for $C_{18}H_{35}Cl_2P$: C, 61.18; H, 9.98. Found: C, 61.11; H, 10.20.

Tricyclohexylphosphonium Chloride (PCy_3·HCl). In a N_2 atmosphere glovebox, PCy_3 (500 mg, 1.78 mmol) and diethyl ether (10 mL) were added to a glass-walled vessel equipped with a vacuum stopcock. A solution of HCl (1 N in ether, 0.445 mL) was added dropwise under N_2. After being stirred for 2 h the reaction suspension was filtered and washed with ether (2 × 10 mL) under N_2. The filtrate was concentrated under vacuum to afford unreacted tricyclohexylphosphine (227 mg, 45%). The filter cake was dried under vacuum to give PCy_3·HCl as a white powder (268 mg, 48%, 87% based on recovered PCy_3). IR (Figure S-2g, Supporting Information): 2935, 2852, 2345 (P−H), 1439, 1299, 931, 884 cm^{-1}. ^1H NMR (400 MHz): δ 8.01 (br d, 1H, J_{P-H} = 490 Hz, P*H*), 2.46 (m, 3H, PC*H*), 2.2−1.2 (m, 30H). ^{31}P NMR (160 MHz): δ 20.6. Anal. Calcd for $C_{18}H_{34}ClP$: C, 68.22; H, 10.81. Found: C, 68.17; H, 11.08.

(*E*)-3-(2-Chlorophenyl)acrylic Acid Methyl Ester.[55] A slurry prepared from (*E*)-3-(2-chlorophenyl)acrylic acid (9.1 g, 50 mmol), concentrated H_2SO_4 (5.8 g, 59 mmol), and MeOH (100 mL) was dissolved by heating to reflux (85 °C). Reflux was continued 2 h, then 80 mL of solvent was removed by distillation (68 °C, 1 atm). After cooling, 80 mL of fresh MeOH was added and the reaction was further refluxed overnight. Most of the solvent was removed by distillation (85 mL, 68 °C, 1 atm) and the remaining cloudy, biphasic material was treated with ether (100 mL) and ice water (100 mL). The ether phase was removed, and the aqueous phase was washed with ether (50 mL). The combined ethereal phases were washed once with water (50 mL), twice with aqueous Na_2CO_3 (1M, 50 mL), and once with brine (50 mL), then dried over Na_2SO_4, filtered, and concentrated under vacuum to give (*E*)-3-(2-chlorophenyl)acrylic acid methyl ester as a clear liquid (9.2 g, 94%). IR: 1716, 1635, 1434, 1318, 1171, 758 cm^{-1}. ^1H NMR (300 MHz): δ 8.08 (d, 1H, J = 15.9 Hz), 7.59 (m, 1H), 7.39 (m, 1H), 7.26 (m, 2H), 6.41 (d, 1H, J = 16.2 Hz), 3.80 (s, 3H). ^{13}C NMR (125 MHz): δ 166.8, 140.6, 134.9, 132.6, 131.0, 130.1, 127.5, 127.0, 120.4, 51.8. Anal. Calcd for $C_{10}H_9ClO_2$: C, 61.08; H, 4.61. Found: C, 61.14; H, 4.52.

(*E*)-3-(2-Chlorophenyl)prop-2-en-1-ol (18). In a two-neck round-bottom flask fitted with an addition funnel and a N_2 inlet, (*E*)-3-(2-chlorophenyl)acrylic acid methyl ester (9.0 g, 46 mmol) was dissolved in CH_2Cl_2 (200 mL). After the reaction solution was cooled to −78 °C DIBAl-H (1M in toluene, 135 mL) was added dropwise over 30 min. The reaction mixture was warmed to 0 °C over 1 h then MeOH (40 mL) was added dropwise, maintaining a steady rate of gas evolution. The reaction mixture was warmed to room temperature and stirred for 30 min before adding Rochelle's salt (saturated aqueous, 150 mL). The resulting layers were stirred vigorously until the solution was clear. The organic phase was removed and the aqueous phase was washed (3 × 150 mL of CH_2Cl_2). The combined organic phases were washed with saturated Na_2SO_4 (150 mL) and brine (150 mL) and then dried over Na_2SO_4, filtered, and concentrated under vacuum. The resulting cloudy, light yellow liquid was distilled (89−91 °C, 0.01 mmHg) (lit. 105−107 °C, 0.5 mmHg)[56] to give **18** as a clear colorless liquid (7.4 g, 96%). IR: 3313 (br), 1470, 1440, 1010, 965, 745 cm^{-1}. ^1H NMR (300 MHz): δ 7.54 (dd, 1H, J = 7.3, 2.0 Hz), 7.36 (dd, 1H, J = 7.6, 1.7 Hz), 7.20 (m, 2H), 7.01 (d, 1H, J = 15.9 Hz), 6.35 (dt, 1H, J = 15.9, 5.6 Hz), 4.37 (dd, 2H, J = 5.6, 1.4 Hz), 1.62 (br s, 1H). ^{13}C NMR (75 MHz): δ 134.8, 133.1, 131.1, 129.7, 128.7, 127.1, 126.9, 126.8, 63.6. Anal. Calcd for C_9H_9ClO: C, 64.11; H, 5.38. Found: C, 64.43; H, 5.63.

Mixture of 1-[(*E*)-3-Bromoprop-1-enyl]-2-chlorobenzene (19) and 1-(1-Bromoallyl)-2-chlorobenzene (20) (94:6). In a round-bottom flask **18** (6.0 g, 36 mmol) was dissolved in CCl_4 (7 mL) under N_2 and the solution was cooled to 0 °C. PBr_3 (3.9 g, 14 mmol) was added dropwise with stirring over 10 min. The reaction mixture was stirred for an additional 30 min and then pipetted onto ice water (40 mL). After an additional 10 min, CH_2Cl_2 (15 mL) was added and the resulting organic phase removed. The aqueous phase was further extracted with CH_2Cl_2 (20 mL). The combined organic phases were washed with saturated $NaHCO_3$ (15 mL) then brine (15 mL), filtered, and concentrated under vacuum. The resulting light yellow liquid (7.9 g, 96%) was found to contain **19** and **20** in a 94:6 ratio by ^1H NMR analysis. This material was used without further purification. IR: 1469, 1435, 1200, 1033, 961, 747, 696 cm^{-1}. **19**: ^1H NMR (300 MHz) δ 7.55 (dd, 1H, J = 7.3, 2.1 Hz), 7.35 (dd, 1H, J = 7.3, 2.0 Hz), 7.23 (m, 2H), 7.05 (d, 1H, J = 15.6 Hz), 6.39 (dt, 1H, J = 15.6, 7.8 Hz), 4.18 (dd, 2H, J = 7.8, 0.7 Hz). **20**: ^1H NMR (300 MHz) δ 7.61 (d, 1H, J = 7.6 Hz), 7.31 (d, 1H, J = 8.4 Hz), 7.22 (m, 2H), 6.28 (m, 1H), 6.08 (d, 1H, J = 7.5 Hz), 5.35 (d, 1H, J = 16.7 Hz), 5.24 (d, 1H, 10.0 Hz). **19**: ^{13}C NMR (75 MHz) δ 133.8, 133.3, 130.3, 129.8, 129.3, 127.8, 127.0, 126.9, 32.9. **20**: ^{13}C NMR (75 MHz) not detected.

3-[(*E*)-3-(2-Chlorophenyl)allyl]-3,4-dihydroquinazoline (21). In a round-bottom flask, **2** (2.6 g, 20 mmol) was dissolved in DMF (40 mL) with stirring under N_2. After the mixture was cooled to 0 °C, K_2CO_3 (5.5 g, 40 mmol) and a solution of **19** and **20** (94:6) (4.6 g, 20 mmol) in DMF (5 mL) were added to the reaction vessel. The reaction mixture was stirred an additional 1 h at 0 °C and then overnight at 25 °C. The resulting suspension was then diluted with THF (120 mL), filtered, and concentrated under vacuum. Analysis of the crude reaction mixture by ^1H NMR indicated a >20:1 ratio of 3,4-dihydro- to 1,4-dihydroquinazoline products. Column chromatography (6:3.5:0.5 → 4.75:4.75:0.5 EtOAc/actone/Et_3N) afforded **21** (3.7 g, 65%) as a pale yellow powder, which was stored under nitrogen until use. IR: 1609, 1593, 1569, 1486, 1165, 971, 762, 746 cm^{-1}. ^1H NMR (300 MHz): δ 7.52 (m, 1H), 7.37 (m, 1H), 7.27−6.97 (m, 7H), 6.86 (d, 1H, J = 7.5 Hz), 6.11 (dt, 1H, J = 15.8, 6.5 Hz), 4.56 (s, 2H), 3.94 (d, 2H, J = 6.5 Hz). ^1H NOESY: Figure S-2h, Supporting Information. ^{13}C NMR (75 MHz): δ 149.9, 141.6, 134.1, 133.1, 131.0, 129.8, 129.2, 128.4, 127.0 (2C), 126.1, 125.7, 124.9, 124.6, 120.3, 55.0, 46.5. Anal. Calcd for $C_{17}H_{15}ClN_2$: C, 72.21; H, 5.35; N, 9.91. Found: C, 72.04; H, 5.56; N, 9.77.

3-(2-Chlorophenyl)-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazoline (23). The reaction was carried out according to the general procedure for intramolecular olefin coupling reactions of DHQs with **21** (1.13 g, 4.00 mmol), $[RhCl(coe)_2]_2$ (143 mg, 0.200 mmol), and ca. 2:1 mixture of Cy-[3.3.1]-Phoban and *exo*-Cy-[4.2.1]-Phoban (135 mg, 0.600 mmol) in 1,2-dichlorobenzene. The reaction tube was heated to 150 °C for 10 h until ^1H NMR indicated that **21** had been completely consumed. Column chromatography eluting with CH_2Cl_2 containing 3.3% of a mixture of 15% NH_4OH in MeOH gave **23** as a tan powder (673 mg, 60%), which was stored under nitrogen until use. If contaminated with trace quinazoline, **23** could be further purified by crystallization (slow vapor diffusion of hexanes into THF). IR: 1625, 1588, 1568, 1479, 1438, 1167, 1037, 760, 721 cm^{-1}. ^1H NMR (300 MHz, C_6D_6): δ 7.39 (d, 1H,

(55) Terrian, D. L.; Mohammad, T.; Morrison, H. *J. Org. Chem.* **1995**, *60*, 1981.

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J = 7.8 Hz), 7.28 (dd, 1H, J = 7.8, 1.6 Hz), 7.20, (dd, 1H, J = 8.0, 1.2 Hz), 7.05 (t, 1H, J = 7.6 Hz), 6.94 (d, 1H, J = 7.4 Hz), 6.88 (d, 1H, J = 7.6 Hz), 6.75 (td, 1H, J = 7.7, 1.6 Hz), 6.71 (d, 1H, J = 7.2 Hz), 4.28 (t, 1H, J = 8.8 Hz), 4.05 (d, 1H, J = 13.2 Hz), 3.96 (d, 1H, J = 13.2 Hz), 2.48 (td, 1H, J = 8.8, 3.5 Hz), 2.33 (q, 1H, J = 8.1 Hz), 1.99 (dddd, 1H, J = 12.7, 9.0, 7.2, 3.5 Hz), 1.46 (dq, 1H, J = 12.6, 8.1 Hz). ^{13}C NMR (125 MHz): δ 162.8, 143.3, 138.7, 134.0, 129.6, 129.1, 128.4, 128.1, 127.1, 125.7, 124.6, 124.1, 119.3, 49.5, 47.4, 46.1, 28.4. Anal. Calcd for $C_{17}H_{15}ClN_2$: C, 72.21; H, 5.35; N, 9.91. Found: C, 72.40; H, 5.40; N, 9.79.

2-(1,2,3,9-Tetrahydropyrrolo[2,1-*b*]quinazolin-3-yl)phenylamine (24). In a N_2 glovebox CuI (84 mg, 0.44 mmol) and (±)-*trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine (126 mg, 0.88 mmol) were combined in 1,4-dioxane (5 mL) and stirred at 25 °C until the CuI completely dissolved. The resulting solution was added to a glass-walled vessel equipped with a vacuum stopcock containing **23** (500 mg, 1.77 mmol), trifluoroacetamide (400 mg, 3.54 mmol), and K_2CO_3 (489 mg, 3.54 mmol). The vessel was then sealed and heated to 140 °C with stirring for 60 h. After being cooled to 0 °C the reaction vessel was opened under N_2, and HCl (6M, 20 mL) was added dropwise. The reaction vessel was then resealed and heated to 75 °C for 9 h. The resulting solution was cooled to 0 °C, basified with NH_4OH, and extracted with ether (40 mL) and CH_2Cl_2 (2 × 40 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated to a brown oil. Purification by column chromatography using gradient elution with CH_2Cl_2 containing 5−10% of a mixture of 10% NH_4OH in MeOH gave **23** (147 mg, 29%) and **24** (171 mg, 37%) as a tan powder. This material exhibited spectroscopic properties consistent with literature data.[36] ^{1}H NMR (400 MHz): δ 7.14−7.08 (m, 2H), 7.05 (td, 1H, J = 7.6, 1.5 Hz), 6.99−6.92 (m, 2H), 6.87 (d, 1H, J = 7.1 Hz), 6.78−6.70 (m, 2H), 4.62 (s, 2H), 4.31 (br s, 2H), 4.15 (dd, 1H, J = 8.6, 5.3 Hz), 3.54 (ddd, 1H, J = 9.6, 7.3, 7.3 Hz), 3.37 (ddd, 1H, J = 9.6, 7.8, 4.6 Hz), 2.51−2.34 (m, 2H).

Dimethyl[2-(1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-3-yl)-phenyl]amine (Vasicoline). The reaction was run following a modified literature procedure.[38] Under a CO atmosphere, $Fe(CO)_5$ (1.24 g, 6.32 mmol) was dissolved in 100% ethanol (5 mL). To this solution was added a degassed solution of KOH (1.13 g, 20.1 mmol) in ethanol (6 mL). The resulting solution was stirred under CO for 2 h. Stirring was then ceased to allow the formed white precipitate ($KHCO_3$) to settle. In a N_2 atmosphere glovebox, 825 μL (470 μmol) of the orange $KHFe(CO)_4$ solution was added to a 10 mL steel Parr reactor containing a Teflon stirbar. A suspension prepared from **24** (50 mg, 190 μmol), formaldehyde (37% aqueous, 77 mg, 950 μmol), and ethanol (1 mL) was also added to the reactor before it was sealed and pressurized to 5 bar with CO. The reactor was heated to 105 °C with stirring for 48 h. After cooling to 25 °C excess CO pressure was released, and the reaction mixture was treated with 6 M HCl (1 mL). Ethanol was removed under reduced pressure. The aqueous reaction mixture was then basified with NH_4OH and extracted with CH_2Cl_2 (3 × 4 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. Column chromatography eluting with CH_2Cl_2 containing 3% of a mixture of 10% NH_4OH in MeOH afforded vasicoline (32 mg, 58%) as a white solid. This material exhibited spectroscopic properties consistent with literature data.[38] Mp 128−130 °C (lit.[32] mp 135 °C). ^{1}H NMR (300 MHz): δ 7.25−6.90 (m, 8H), 4.71 (d, 1H, J = 13.4 Hz), 4.64 (d, 1H, J = 13.5 Hz), 4.56 (dd, 1H, J = 9.2, 7.5 Hz), 3.45−3.30 (m, 2H), 2.72 (s, 6H), 2.56 (dddd, 1H, J = 12.5, 9.3, 7.7, 4.8 Hz), 1.96 (dtd, 1H, J = 12.7, 7.8, 7.3 Hz). ^{13}C NMR (75 MHz): δ 165.1, 153.3, 143.6, 137.7, 129.1, 128.4, 127.9, 125.8, 124.7, 124.6, 123.9, 121.0, 119.5, 50.3, 47.7, 46.2, 44.0, 30.0.

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Supporting Information Available: Procedural details and analytical data for all new compounds not included in the Experimental Section and various characteristic spectra mentioned in Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org..

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