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Reversible P(III)/P(V) Redox: Catalytic Aza-Wittig Reaction for the Synthesis of 4(3*H*)-Quinazolinones and the Natural Product Vasicinone

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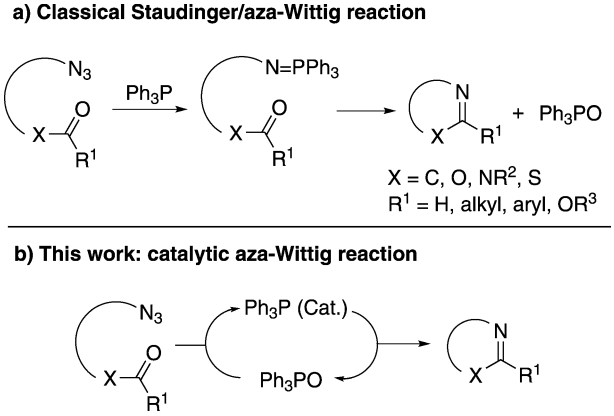
Abstract: The catalytic aza-Wittig reaction based on a phosphine/phosphine oxide catalytic cycle is reported. The by-product triphenylphosphine oxide (Ph_3PO) was reduced *in situ* to triphenylphosphine (Ph_3P) with good chemselectivity so that the aza-Wittig reaction can be accomplished by using merely a catalytic amount of triphenylphosphine. The reaction has been demonstrated in an efficient synthesis of 4(3*H*)-quinazolinones and the natural product (*S*)-vasicinone in high yields, by using a catalytic amount of triphenylphosphine (5%) and the tetramethyldisiloxane/titanium tetraisopropoxide [TMDS/Ti(O-*i*-Pr)$_4$] reductant system (81–95% yields and >99% *ee*).

Keywords: catalytic aza-Wittig reaction; phosphine redox cycle; 4(3*H*)-quinazolinones; tetramethyldisiloxane; vasicinone

Analogously to the Wittig reaction,[1] the aza-Wittig reaction of iminophosphoranes with carbonyl compounds provides a powerful method to construct C=N double bonds.[2] It has become a useful tool in the construction of various five-, six- and seven-membered nitrogen heterocycles *via* inter- or intramolecular processes under mild and neutral reaction conditions.[3] A series of natural products has also been prepared by using the aza-Wittig reaction as the key step, usually with complete retention of the stereochemistry.[4] Nevertheless, triphenylphosphine oxide is produced in stoichiometric amounts as a waste (resulting in low atom efficiency) during the aza-Wittig reaction. And in some cases, the separation of the product from this by-product (Ph_3PO) is problematic (Scheme 1a).[5] Therefore, the development of a catalytic aza-Wittig reaction with recycling of the by-product Ph_3PO is highly desirable (Scheme 1b).



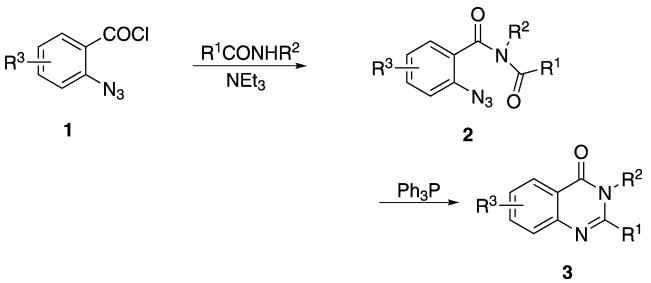
Scheme 1. Synthesis of nitrogen heterocycles by classical and phosphine-catalyzed aza-Wittig reactions.

Phosphine oxide can be reduced to phosphine by some highly toxic or sensitive reducing agents, such as phosgene,[6] trichlorosilane[7] or lithium aluminum hydride,[8] which are not suitable for the catalytic aza-Wittig reaction due to the harsh reaction conditions and poor functional group tolerance. Silanes such as Ph_2SiH_2, $(EtO)_3SiH$/Ti(O-*i*-Pr)$_4$ have been used to reduce phosphine oxides to phosphines with good yield and chemselectivity.[9] However, $(EtO)_3SiH$ has been found to be harmful since it produces the dangerous and toxic SiH_4 gas. The more stable tetramethyldisiloxane (TMDS, $Me_2HSiOSiMe_2H$), easily obtained as an inexpensive by-product from the organosilicon industry (~50 US $/1000 g in China), was recently utilized as a general and selective reducing agent for phosphine oxides under the catalysis of Ti(O-*i*-Pr)$_4$,[10] $Cu(CF_3COO)_2$,[11] or InBr[12] under mild reaction conditions. Some silanes have been successfully used in catalytic Wittig,[13] Appel,[14] and Staudinger reactions[15] as well as in the reduction of silyl

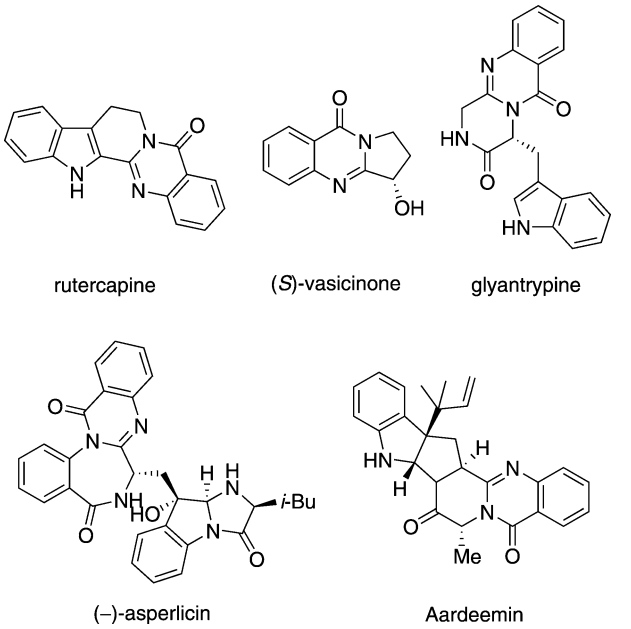
peroxides[16] by using catalytic amounts of a phosphine. Although a catalytic aza-Wittig reaction was also reported by Marsden et al.,[17] the method they reported is based on the reaction of carbonyl-containing isocyanates with catalytic amounts of cyclic phosphine oxide, and the reaction occurs solely at the P(V) oxidation state. Moreover the starting materials – isocyanates – they used are labile, harmful and not easily accessible. So the development of a variant of the classical catalytic Staudinger/aza-Wittig reaction based on the phosphine(III)/phosphine(V) oxide catalytic cycle (Scheme 1b) would represent a significant advance, because the starting materials – azides – are easily accessible with structural diversity. Recently we became interested in the synthesis of various nitrogen heterocycles *via* conventional aza-Wittig reactions.[18] Herein we wish to report an example of a catalytic aza-Wittig reaction based on the phosphine/phosphine oxide catalytic cycle for an efficient synthesis of 4(3*H*)-quinazolinones and the natural product vasicinone.

The quinazolinone heterocycle is an important structural motif in many natural products, drugs, and biologically active compounds. More than 150 natural products containing the quinazolinone core have been reported.[19] Eguchi and co-workers have reported a general synthesis for a variety of 4(3*H*)-quinazolinones by an intramolecular aza-Wittig reaction through the reactive imide carbonyl groups (Scheme 2).[20] Owing to its mild neutral conditions and good yields, this protocol was then utilized successfully in the synthesis of many natural products containing the quinazolinone skeleton, such as rutecarpine, tryptanthrin,[21] ardeemin,[22] vasicinone,[23] benzomalvin A,[24] asperlicin,[25] and glyantrypine[26] (Scheme 3).

A stoichiometric quantity of triphenylphosphine was used in the above synthetic method. Our idea is that if a catalytic amount of triphenylphosphine was used in the presence of the TMDS/Ti(O-*i*-Pr)$_4$ reductant system, could we realize the catalytic aza-Wittig reaction. Initially, we selected the azide **2a** as the reactant. Since triphenylphosphine oxide can be reduced under refluxing toluene conditions in the presence of silane, the thermal stability of azide **2a** was first checked. To our surprise, the azide **2a** was very stable under refluxing toluene conditions: it was completely recovered even after being refluxed in toluene for 24 h. Then the catalytic aza-Wittig reaction of **2a** was carried out: when a mixture of the azide **2a**, a catalytic amount of triphenylphosphine (20% equiv.), TMDS and Ti(O-*i*-Pr)$_4$ (100% equiv.) was refluxed in toluene, we were pleased to find that a high yield of the 4(3*H*)-quinazolinone **3a** was obtained (Table 1, entry 1) within a short reaction time (0.5 h). In the case that the amount of Ti(O-*i*-Pr)$_4$ was reduced from 100% to 10% equiv., satisfactory yields (91–93%, Table 1, entries 1–3) were also obtained when the reaction time was increased from 0.5 h to 8 h. When the

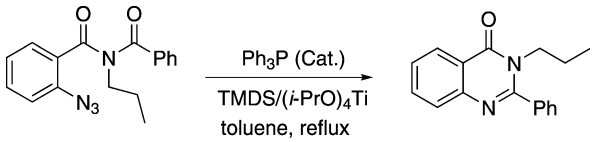


Scheme 2. Literature preparation of 4(3*H*)-quinazolinones by intramolecular aza-Wittig reaction.



Scheme 3. Some natural products prepared by Eguchi's protocol.

Table 1. Optimization of the reaction conditions.

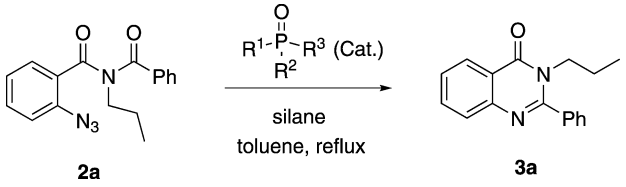


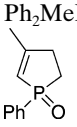
2a **3a**

Entry	Ti(O-*i*-Pr)$_4$	Ph_3P	Reaction Time [h]	Yield[a] [%]
1	100%	20%	0.5	91
2	25%	20%	2	93
3	10%	20%	8	91
4	10%	10%	14	94
5	10%	5%	24	95
6	10%	0	24	0

[a] Isolated yields.

Table 2. Optimization of the reaction conditions.



	Silane	$Ti(O\text{-}i\text{-}Pr)_4$	$R^1\text{-}P(=O)(R^2)\text{-}R^3$	Reaction Time [h]	Yield[a] [%]
1	TMDS	0	Ph_3PO (20%)	24	0
2	Ph_2SiH_2	0	Ph_3PO (20%)	24	0
3	Ph_3SiH	0	Ph_3PO (20%)	24	0
4	Et_3SiH	0	Ph_3PO (20%)	24	0
5	TMDS	10%	Ph_3PO (5%)	24	94
6	TMDS	10%	Ph_2MePO (5%)	24	92
7	TMDS	10%	 (5%)	24	91
8	TMDS	10%	 (5%)	24	92

[a] Isolated yields.

amount of Ph_3P was reduced from 20% to 5% equiv., the reaction gave high yields of the product (91–95%, Table 1, entries 3–5) with prolongation of the reaction time from 8 h to 24 h. However, no 4(3*H*)-quinazolinone **3a** was produced in the absence of Ph_3P (Table 1, entry 6).

The phosphine oxide was also directly used in the above catalytic aza-Wittig reaction (Table 2). In these cases, the phosphine oxide may be regarded as a pre-catalyst for the reaction. However, in the absence of $Ti(O\text{-}i\text{-}Pr)_4$, no 4(3*H*)-quinazolinone **3a** was produced (Table 2, entries 1-4) irrespective of whether TMDS, Ph_2SiH_2, Ph_3SiH, or Et_3SiH was used as a reductant. In the presence of the catalyst $Ti(O\text{-}i\text{-}Pr)_4$, 4(3*H*)-quinazolinone **3a** was obtained in high yield (94%, Table 2, entry 5) when Ph_3PO (5%) and TMDS were used. The influence of different phosphine oxides on the above catalytic aza-Wittig reaction was further investigated. As indicated in Table 2, no obvious differences among various phosphine oxide were observed when the TMDS/$Ti(O\text{-}i\text{-}Pr)_4$ reductant system was utilized, and high yields (91–94%) of the product were reached with all the phosphine oxides used when the reaction mixture was refluxed for 24 h (Table 2, entries 5–8).

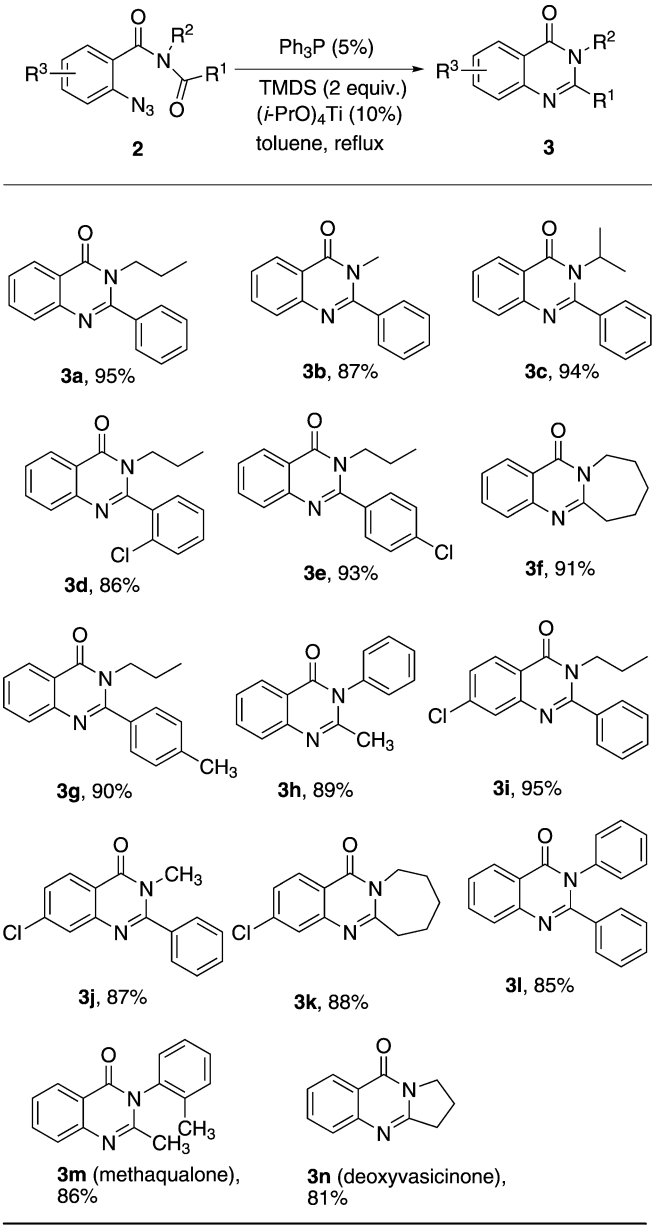
By using triphenylphosphine in a catalytic amount (5%), various azides **2** were then employed for the reaction with TMDS/$Ti(O\text{-}i\text{-}Pr)_4$ as reductant system (Table 3). All reactions proceeded smoothly to give the corresponding 4(3*H*)-quinazolinones **3** (Table 3) in 81–95% yields regardless of the electronic properties and steric hindrance of the substituents on azides **2**.

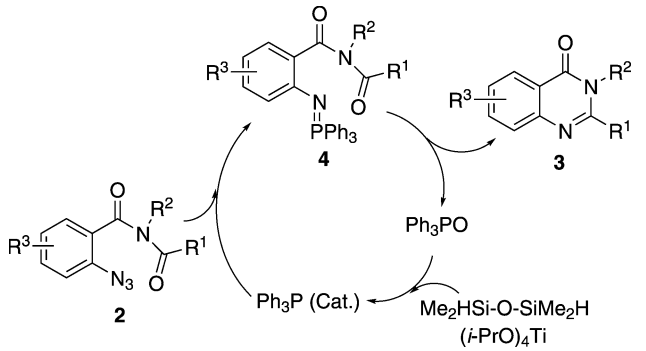
A possible mechanism for the catalytic aza-Wittig reaction can be proposed (Scheme 4). It presumably involves (i) a Staudinger reaction of azide **2** with triphenylphosphine to give the iminophosphorane **4**; (ii) intramolecular aza-Wittig reaction of iminophosphorane **4** through the imide carbonyl group to produce the 4(3*H*)-quinazolinone **3** and triphenylphosphine oxide; (iii) reduction of triphenylphosphine oxide by the TMDS/$Ti(O\text{-}i\text{-}Pr)_4$ system to regenerate triphenylphosphine, which enters a new catalytic cycle.

Vasicinone, known as one of the quinazolinone alkaloids separated from the leaves and the inflorescene of *Adhatada vasica* Nees, has been prepared by using a conventional aza-Wittig reaction as the key step.[23] The above catalytic aza-Wittig reaction was then utilized in preparing optically active (*S*)-vasicinone (Scheme 5). The azide **5**, obtained from 2-azidobenzoyl chloride **1** and 3-(*tert*-butyldimethylsiloxy)-γ-lactam according to literature report, was refluxed in toluene for 24 h in the presence of Ph_3P (5%) and the TMDS/$Ti(O\text{-}i\text{-}Pr)_4$ system to give *O*-*tert*-butydimethylsilylvasicinone **6**. Further deprotection of the siloxy substituent by tetrabutylammonium fluoride produced (*S*)-vasicinone **7** in 84% yield with >99% *ee*.

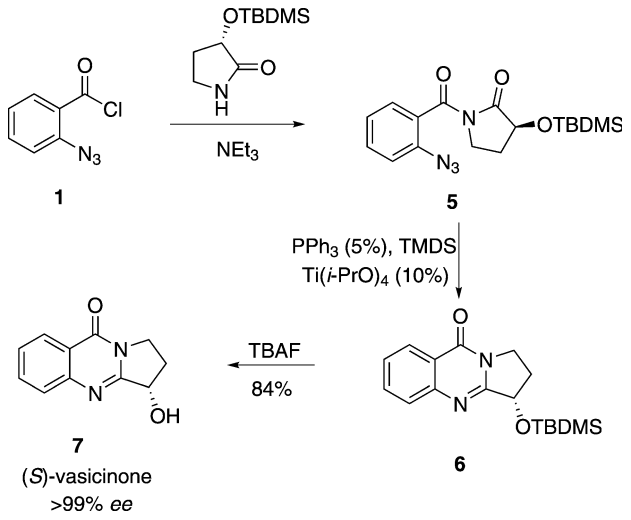
In conclusion, the catalytic aza-Wittig reaction based on a phosphine(III)/phosphine(V) oxide catalytic cycle has been developed.[27] A variety of 4(3*H*)-quinazolinones was obtained *via* the catalytic aza-Wittig reaction with triphenylphosphine used in a cata-

Table 3. Preparation of 4(3*H*)-quinazolinones **3** by the catalytic aza-Wittig reaction.





Scheme 4. A possible mechanism for the catalytic aza-Wittig reaction.



Scheme 5. Preparation of natural product (*S*)-vasicinone (**7**).

lytic amount, and the air-stable and inexpensive tetramethyldisiloxane TMDS/Ti(O-*i*-Pr)$_4$ being used as a reductant. This protocol also facilitated the synthesis of some medicinal and natural products such as methaqualone, deoxyvasicinone and (*S*)-vasicinone with >99% *ee*.

Experimental Section

General Methods

Melting points are uncorrected. HR-MS were measured on an Agilent 6224 TOF LC/MS spectrometer. ^{1}H NMR were recorded in $CDCl_3$ on a Varian Mercury 400 or 600 spectrometer and resonances relative to TMS. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR spectra were recorded on Varian Mercury 400/600 (100/150 MHz) instruments with complete proton decoupling ($CDCl_3$: 77.0 ppm). Enantiomeric ratios were determined by chiral HPLC on an Agilent 1100 series system with chiral columns (chiralpak AD-H column,) with hexane and *i*-PrOH (80:20) as solvents (temp., 25 °C; flow, 0.70 mL/min; λ, 254 nm). Substrates **2** were synthesized according to the literature.[20]

General Procedure for the Preparation of 4(3*H*)-Quinazolinone 3 *via* Catalytic Aza-Wittig Reaction

To a solution of azide **2**[20] (2 mmol) in toluene (10 mL) was added Ph_3P (0.026 g, 0.1 mmol). After the reaction mixture had been stirred for 10 min, Ti(O-*i*-Pr)$_4$ (0.053 g, 0.2 mmol) and TMDS (0.54 g, 4 mmol) were added sequentially. The reaction mixture was then stirred at 110 °C and monitored by TLC. After the reaction was completed (24–48 h), the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (ether/petroleum ether = 1:4, v/v) to give 4(3*H*)-quinazolinone **3**.

2-Phenyl-3-propyl-4(3*H*)-quinazolinone (3a): White solid; mp 99–101 °C (Lit.[28] mp 98–100 °C); ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 8.34 (d, J = 7.8 Hz, 1H, Ar-H), 7.77–7.73 (m, 2H, Ar-H), 7.52–7.49 (m, 6H, Ar-H), 3.95 (t, J = 7.8 Hz, 2H, NCH_2), 1.67–1.61 (m, 2H, CH_2), 0.77 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 161.9, 156.1, 147.0, 135.4, 134.1, 129.6, 128.6, 127.6, 127.2, 126.8, 126.6, 120.7, 47.3, 21.9, 11.0.

3-Methyl-2-phenyl-4(3*H*)-quinazolinone (3b): White solid; mp 130–132 °C (Lit.[29] mp 130–132 °C); ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 8.33 (d, J = 7.8 Hz, 1H, Ar-H), 7.75–7.73 (m, 2H, Ar-H), 7.57–7.48 (m, 6H, Ar-H), 3.49 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.3, 155.8, 146.9, 135.1, 133.9, 129.7, 128.5, 127.7, 127.1, 126.6, 126.3, 120.1, 33.9.

3-Isopropyl-2-phenyl-4(3*H*)-quinazolinone (3c): White solid; mp 139–141 °C (Lit.[30] mp 133–135 °C); ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 8.31 (d, J = 8.4 Hz, 1H, Ar-H), 7.75–7.70 (m, 2H, Ar-H), 7.52–7.48 (m, 6H, Ar-H), 4.37–4.31 (m, 1H, NCH), 1.59 (d, J = 7.2 Hz, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.3, 156.4, 146.6, 136.2, 133.9, 129.5, 128.7, 128.6, 127.0, 126.7, 126.2, 121.9, 53.8, 19.4.

2-(2-Chlorophenyl)-3-propyl-4(3*H*)-quinazolinone (3d): White solid; mp 114–116 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 8.36 (d, J = 7.8 Hz, 1H, Ar-H), 7.79–7.74 (m, 2H, Ar-H), 7.54–7.43 (m, 5H, Ar-H), 4.25–4.20 (m, 1H, NCH), 3.49–3.44 (m, 1H, NCH), 1.73–1.68 (m, 1H, CH), 1.53–1.47 (m, 1H, CH), 0.76 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 161.5, 153.2, 146.9, 134.2, 134.0, 132.1, 130.9, 129.6, 129.5, 127.2, 127.1, 127.0, 126.5, 120.9, 46.8, 21.6, 11.0; HR-MS: m/z = 299.0951, calculated for $[C_{17}H_{15}ClN_2O+H]^+$: 299.0951.

2-(4-Chlorophenyl)-3-propyl-4(3*H*)-quinazolinone (3e): White solid; mp 72–74 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 8.33 (d, J = 7.8 Hz, 1H, Ar-H), 7.78–7.70 (m, 2H, Ar-H), 7.53–7.48 (m, 5H, Ar-H), 3.94 (t, J = 7.8 Hz, 2H, NCH_2), 1.65–1.60 (m, 2H, CH_2), 0.79 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 161.8, 154.9, 146.8, 135.8, 134.2, 133.8, 129.1, 128.9, 127.2, 127.0, 126.6, 120.7, 47.3, 21.9, 11.0; HR-MS: m/z = 299.0946, calculated for $[C_{17}H_{15}ClN_2O+H]^+$: 299.0951.

7,8,9,10-Tetrahydroazepino[2,1-*b*]quinazolin-12(6*H*)-one (3f): White solid; mp 96–97 °C (Lit.[31] mp 95–97 °C); ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 8.26 (dd, J = 7.8 Hz, 1H, Ar-H), 7.73–7.43 (m, 3H, Ar-H), 4.42–4.38 (m, 2H, NCH_2), 3.08 (t, J = 5.4 Hz, 2H, CH_2), 1.89–1.82 (m, 6H, $3CH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 161.4, 159.4, 146.8, 133.7, 126.6, 126.2, 126.0, 119.8, 42.5, 37.2, 29.2, 27.7, 25.0.

3-Propyl-2-(*para*-tolyl)-4(3*H*)-quinazolinone (3g): White solid; mp 104–105 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 8.32 (d, J = 7.2 Hz, 1H, Ar-H), 7.75–7.72 (m, 2H, Ar-H), 7.51–7.31 (m, 5H, Ar-H), 3.96 (t, J = 7.8 Hz, 2H, NCH_2), 2.44 (s, 3H, CH_3), 1.66–1.62 (m, 2H, CH_2), 0.78 (t, J = 7.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 161.9, 156.1, 146.9, 139.5, 133.9, 132.5, 129.1, 127.4, 127.1, 126.5, 126.4, 120.6, 47.2, 21.8, 21.2, 10.9; HR-MS: m/z = 279.1505, calculated for $[C_{18}H_{18}N_2O+H]^+$: 279.1497.

2-Methyl-3-phenyl-4(3*H*)-quinazolinone (3h): White solid; mp 149–151 °C (Lit.[28] mp 147–149 °C); ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 8.28 (d, J = 7.8 Hz, 1H, Ar-H), 7.78–7.46 (m, 6H, Ar-H), 7.27 (d, J = 8.4 Hz, 2H, Ar-H), 2.25 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 161.9, 153.9, 147.1, 137.5, 134.2, 129.7, 129.0, 127.8, 126.7, 126.4, 126.3, 120.4, 24.1.

7-Chloro-2-phenyl-3-propyl-4(3*H*)-quinazolinone (3i): White solid; mp 96–97 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 8.25 (d, J = 9.0 Hz, 1H, Ar-H), 7.72 (s, 1H, Ar-H), 7.53–7.44 (m, 6H, Ar-H), 3.93 (t, J = 7.8 Hz, 2H, NCH_2), 1.66–1.60 (m, 2H, CH_2), 0.76 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 161.4, 157.4, 148.0, 140.3, 135.1, 129.9, 128.7, 128.2, 127.6, 127.4, 126.8, 119.2, 47.5, 21.9, 11.0; HR-MS: m/z = 299.0952, calculated for $[C_{17}H_{15}ClN_2O+H]^+$: 299.0951.

7-C hloro-3-methyl-2-phenyl-4(3*H*)-quinazolinone (3j): White solid; mp 166–168 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 8.26 (d, J = 8.4 Hz, 1H, Ar-H), 7.74 (s, 1H, Ar-H), 7.57–7.44 (m, H, Ar-H), 3.49 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 161.9, 157.2, 148.1, 140.3, 134.9, 130.2, 128.8, 128.0, 127.8, 127.4, 126.9, 118.8, 34.2; HR-MS: m/z = 271.0633, calculated for $[C_{15}H_{11}ClN_2O+H]^+$: 271.0638.

3-Chloro-7,8,9,10-tetrahydroazepino[2,1-*b*]quinazolin-12(6*H*)-one (3k):White solid; mp 111–113 °C (Lit.[32] mp 101–104 °C); ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 8.17 (d, J = 8.4 Hz, 1H, Ar-H), 7.60 (s, 1H, Ar-H), 7.38 (d, J = 8.4 Hz, 1H, Ar-H), 4.37 (t, J = 4.2 Hz, 2H, NCH_2), 3.06 (t, J = 5.4 Hz, 2H, CH_2), 1.88–1.77 (m, 6H, $3CH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 160.8, 160.7, 147.9, 139.7, 128.1, 126.5, 125.9, 118.3, 42.6, 37.4, 29.2, 27.6, 24.9.

2,3-Diphenyl-4(3*H*)-quinazolinone (3l): White solid; mp 158–160 °C (Lit.[30] mp 158–159 °C); ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 8.36 (d, J = 7.8 Hz, 1H, Ar-H), 7.84–7.80 (m, 2H, Ar-H), 7.55–7.52 (m, 1H, Ar-H), 7.34–7.20 (m, 8H, Ar-H), 7.15 (d, J = 7.8 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.1, 155.0, 147.3, 137.5, 135.2, 134.6, 129.1, 128.9, 128.8, 128.3, 127.8, 127.5, 127.1, 127.0, 120.7.

2-Methyl-3-(*ortho*-tolyl)-4(3*H*)-quinazolinone (3m): White solid; mp 116–118 °C (Lit.[33] mp 114–115 °C); ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 8.29 (d, J = 8.4 Hz, 1H, Ar-H), 7.78 (t, J = 7.8 Hz, 1H, Ar-H), 7.70 (d, J = 8.4 Hz, 1H, Ar-H), 7.48 (t, J = 7.2 Hz, 1H, Ar-H), 7.41–7.38 (m, 3H, Ar-H), 7.16 (d, J = 7.8 Hz, 1H, Ar-H), 2.19 (s, 3H, CH_3), 2.13 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 161.4, 154.1, 147.4, 136.6, 135.1, 134.4, 131.3, 129.4, 127.7, 127.5, 126.9, 126.6, 126.4, 120.5, 23.7, 17.2.

2,3-Dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (3n): White solid; mp 110–111 °C (Lit.[31] mp 109 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.27 (d, J = 8.0 Hz, 1H, Ar-H), 7.74–7.42 (m, 3H, Ar-H), 4.20 (t, J = 7.2 Hz, 2H, NCH_2), 3.17 (t, J = 8.0 Hz, 2H, CH_2), 2.33–2.23 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 160.8, 159.3, 149.0, 134.0, 126.7, 126.2, 126.1, 120.3, 46.4, 32.4, 19.4.

Preparation of the Natural Product (*S*)-Vasicinone (7)

To a solution of azide **5**[23] (0.72 g, 2 mmol) in toluene (10 mL) was added Ph_3P (0.026 g, 0.1 mmol). After the reaction mixture had been stirred for 10 min, Ti(O-*i*-Pr)$_4$ (0.053 g, 0.2 mmol) and TMDS (0.54 g, 4 mmol) was added sequentially. The reaction mixture was stirred at 110 °C and monitored by TLC. After the reaction was completed (24 h), the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (ether/petroleum ether = 1:4 v/v) to give 4(3*H*)-quinazolinone **6**.

To the solution of **6** in THF (10 mL), was added TBAF (0.52 g, 2 mmol) at 0 °C, and the mixture was stirred for 15 h at room temperature. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (AcOEt as the eluent) to give (*S*)-vasicinone **7**; yield: 84%, >99% *ee*.

(*S*)-2,3-Dihydro-3-hydroxypyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (7): White solid; mp 201–203 °C (Lit.[23] mp 200–202 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.30 (d, J = 7.6 Hz, 1H, Ar-H), 7.78–7.48 (m, 3H, Ar-H), 5.50 (br, 1H, OH), 5.25 (t, J = 7.6 Hz, 1H, OCH), 4.40–4.34 (m, 1H, NCH), 4.05–3.98 (m, 1H, NCH), 2.72–2.26 (m, 2H, CH_2); ^{13}C NMR (DMSO-d_6, 150 MHz): δ = 160.6, 159.9, 149.1, 134.2, 127.0, 126.4, 125.8, 120.6, 71.4, 43.1, 29.6. The *ee* was determined by chiral GC using a chiralpak AD-H column; t_{major} = 13.1 min, t_{minor} = 12.4 min (>99% *ee*).

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