Rh(III)-Catalyzed [5+1] Oxidative Cycloaddition of Arylguanidines with Alkynes: A Novel Access to C4-Disubstituted 1,4-Dihydroquinazolin-2-amines

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1. General experimental procedures

All reactions were performed under an inert atmosphere of argon and with anhydrous solvents in glassware oven or flame dried at 80 °C unless otherwise stated. All chemicals were purchased from Acros Organics Ltd., Aldrich Chemical Co. Ltd., Alfa Aesar, Fluorochem Ltd., Strem Chemicals Inc. or TCI Europe N.V. chemical companies and used without further purification, unless otherwise stated.

Analytical thin layer chromatography was carried out on silica-coated aluminium plates (silica gel 60 F254 Merck) or on aluminium sheets (aluminium oxide 60 F254 neutral Merck) using UV light as visualizing agent (254 nm) and KMnO4 (solution of 1.5 g of potassium permanganate, 10 g of potassium bicarbonate and 1.25 mL of 10% sodium hydroxide in 200 mL of water) with heat as developing agents. Flash column chromatography was performed on silica gel 60 (Merck, 230-400 mesh) or aluminium oxide Camag Brockmann I neutral (Fisher Chemical, 100-250 mesh) with the indicated eluent.

Mass spectrometry was carried out on a Bruker microTOF spectrometer.

1H- and 13C-NMR experiments were carried out using a Varian Inova 500MHz, a Varian Inova 400MHz or a Varian Mercury 300MHz NMR spectrometers and chemical shifts are reported relative to tetramethylsilane and trichloro-fluoro-methane as internal references. Coupling constants \( J \) are given in Hertz (Hz). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p=pentet, m = multiplet or as a combination of them. Multiplicities of 13C NMR signals were determined by DEPT experiments.

All other reagents and solvents: dichloromethane, dichloroethane, tetrahydrofurane, toluene, tPrOH and dimethyleter (99.5-99.8%, GC) were used dry, unless otherwise indicated. Acetone was distilled from K2CO3 and storage over 4Å molecular sieves.

Yields refer to isolated compounds estimated to be > 95% pure as determined by 1H NMR and capillary GC analysis.
2. Preparation of starting materials

2.1. Preparation of guanidines (1)

Guanidines 1a, 1a’, 1b, 1e, 1f, 1h, 1i, 1ba, 1ha and 1ia were analogously prepared following the described procedure for amidine synthesis\textsuperscript{S1} from commercially available \textit{N}-methyleneanilines and the corresponding arylcyanamides.

Guanidines 1c, 1d, 1g, 1ca and 1ga were prepared following the described procedure\textsuperscript{S1} from the corresponding \textit{N}-methyleneaniline hydrochlorides and arylcyanamides.

\textbf{\textit{N,N’}-Dimethyl-\textit{N,N’}-diphenylguanidine (1a)}

\begin{center}
\includegraphics[width=0.2\textwidth]{guanidine1a.png}
\end{center}

According to the literature procedure,\textsuperscript{S1} the guanidine 1a was synthesized in 66 \% yield as a yellow oil (DCM/MeOH 0.90:0.10, \textit{Rf} 0.44).

\textbf{\textit{H NMR}} (300 MHz, CDCl3), \(\delta\) (ppm): 7.2-7.1 (m, 4H), 7.0-6.8 (m, 6H), 5.55 (bs, 1H), 3.11 (s, 6H).

\textbf{\textit{C NMR, DEPT}} (75 MHz, CDCl3), \(\delta\) (ppm): 162.3 (C), 145.9 (2xC), 128.6 (4xCH), 123.3 (2xCH), 122.7 (4xCH), 38.8 (2xCH\textsubscript{3}).
**N,N'-Dimethyl-N,N'-bis(4-methylphenyl)guanidine (1b)**

![1b]

According to a conveniently modified literature procedure, the guanidine 1b was synthesized in 77% yield as a brown oil (DCM/MeOH 0.85:0.15, Rf 0.57).

**1H NMR** (300 MHz, CDCl₃), δ (ppm): 7.01 (d, J = 8.5 Hz, 4H), 6.87 (d, J = 8.5 Hz, 4H), 3.09 (s, 6H), 2.27 (s, 6H).

**13C NMR, DEPT** (75 MHz, CDCl₃), δ (ppm): 163.1 (C), 143.9 (2xC), 133.3 (2xC), 129.6 (4xCH), 123.2 (4xCH), 39.3 (2xCH₃), 20.9 (2xCH₃).

**N,N'-Bis(4-methoxyphenyl)-N,N'-dimethylguanidine (1c)**

![1c]

According to literature procedure, the guanidine 1c was synthesized in 30% yield as a yellow oil (DCM/MeOH 0.95:0.05, Rf 0.53).

**1H NMR** (300 MHz, CDCl₃), δ (ppm): 6.74 (d, J = 8.9 Hz, 4H), 6.65 (d, J = 8.9 Hz, 4H), 6.13 (bs, 1H), 3.68 (s, 6H), 3.08 (s, 6H).

**13C NMR, DEPT** (75 MHz, CDCl₃), δ (ppm): 162.8 (C), 156.6 (2xC), 139.1 (2xC), 125.7 (4xCH), 114.1 (4xCH), 55.4 (2xCH₃), 40.3 (2xCH₃).

**N,N'-Bis(4-chlorophenyl)-N,N'-dimethylguanidine (1d)**

![1d]

According to the literature procedure, the guanidine 1d was synthesized in 89% yield as a yellow oil (DCM/MeOH 0.90:0.10, Rf 0.64).

**1H NMR** (300 MHz, CDCl₃), δ (ppm): 7.1-7.0 (m, 4H), 6.8-6.7 (m, 4H), 5.60 (bs, 1H), 3.12 (s, 6H).

**13C NMR, DEPT** (75 MHz, CDCl₃), δ (ppm): 161.7 (C), 144.5 (2xC), 129.1 (2xC), 129.0 (4xCH), 124.3 (4xCH), 39.2 (2xCH₃).
Dimethyl 4,4’-[(iminomethylene)bis(methylimino)]dibenzoate (1e)

According to the literature procedure, the guanidine 1e was synthesized in 40% yield as a yellow oil (DCM/MeOH 0.90:0.10, \( R_f \) 0.33).

\[ ^1H \text{ NMR} \ (300 \text{ MHz, CDCl}_3), \delta \ (\text{ppm}): \ 7.9-7.8 \ (\text{m, 4H}), \ 7.0-6.9 \ (\text{m, 4H}), \ 3.85 \ (\text{s, 6H}), \ 3.21 \ (\text{s, 6H}). \]

\[ ^{13}C \text{ NMR, DEPT} \ (75 \text{ MHz, CDCl}_3), \delta \ (\text{ppm}): \ 166.7 \ (2\times\text{CO}), \ 160.7 \ (\text{C}), \ 149.4 \ (2\times\text{C}), \ 130.7 \ (4\times\text{CH}), \ 124.4 \ (2\times\text{C}), \ 120.4 \ (4\times\text{CH}), \ 52.1 \ (2\times\text{CH}_3), \ 38.3 \ (2\times\text{CH}_3). \]

N,N’-Dimethyl-N,N’-bis(3-methylphenyl)guanidine (1f)

According to the literature procedure, the guanidine 1f was synthesized in 95% yield as a yellow oil (DCM/MeOH 0.90:0.10, \( R_f \) 0.25).

\[ ^1H \text{ NMR} \ (300 \text{ MHz, CDCl}_3), \delta \ (\text{ppm}): \ 7.1-7.0 \ (\text{m, 2H}), \ 6.9-6.7 \ (\text{m, 6H}), \ 5.22 \ (\text{bs, 1H}), \ 3.13 \ (\text{s, 6H}), \ 2.25 \ (\text{s, 6H}). \]

\[ ^{13}C \text{ NMR, DEPT} \ (75 \text{ MHz, CDCl}_3), \delta \ (\text{ppm}): \ 162.7 \ (\text{C}), \ 146.1 \ (2\times\text{C}), \ 138.7 \ (2\times\text{C}), \ 128.7 \ (2\times\text{CH}), \ 124.5 \ (2\times\text{CH}), \ 123.9 \ (2\times\text{CH}), \ 120.2 \ (2\times\text{CH}), \ 39.2 \ (2\times\text{CH}_3), \ 21.5 \ (2\times\text{CH}_3). \]
\[ N,N'\text{-Bis(3-methoxyphenyl)}-N,N'\text{-dimethylguanidine (1g)} \]

\[
\begin{array}{c}
\text{MeO} \quad \text{N} \quad \text{N} \quad \text{NH} \\
\text{Me} \quad \text{O}_\text{Me} \\
\text{1g}
\end{array}
\]

According to the literature procedure,\textsuperscript{S2} the guanidine 1g was synthesized in 59 \% yield as a yellow oil (DCM/MeOH 0.85:0.15, \( R_f 0.44 \)).

\textbf{\( ^1H \text{ NMR} \)} (300 MHz, CDCl\textsubscript{3}), \( \delta \) (ppm): 7.09 (t, \( J = 8.1 \) Hz, 2H), 6.58 (ddd, \( J = 8.1, 2.2, 0.9 \) Hz, 2H), 6.53 (ddd, \( J = 8.1, 2.2, 0.9 \) Hz, 2H), 6.49 (t, \( J = 2.2 \) Hz, 2H), 3.69 (s, 6H), 3.13 (s, 6H).

\textbf{\( ^{13}C \text{ NMR, DEPT} \)} (75 MHz, CDCl\textsubscript{3}), \( \delta \) (ppm): 162.1 (C), 160.3 (2xC), 147.3 (2xC), 129.6 (2xCH), 115.1 (2xCH), 109.1 (2XCH), 108.6 (2xCH), 55.4 (2xCH\textsubscript{3}), 39.0 (2xCH\textsubscript{3}).

\[ N,N'\text{-Dimethyl-N,N'-bis[3-(trifluoromethyl)phenyl]guanidine (1h)} \]

\[
\begin{array}{c}
\text{F}_3\text{C} \quad \text{N} \quad \text{N} \quad \text{CF}_3 \\
\text{1h}
\end{array}
\]

According to the literature procedure,\textsuperscript{S1} the guanidine 1h was synthesized in 83 \% yield as a brown oil (DCM/MeOH 0.85:0.15, \( R_f 0.46 \)).

\textbf{\( ^1H \text{ NMR} \)} (300 MHz, CDCl\textsubscript{3}), \( \delta \) (ppm): 7.3-7.1 (m, 4H), 7.0-6.9 (m, 4H), 3.32 (s, 6H).

\textbf{\( ^{19}F \text{ NMR} \)} (300 MHz, CDCl\textsubscript{3}), \( \delta \) (ppm): -63.2.

\textbf{\( ^{13}C \text{ NMR, DEPT} \)} (75 MHz, CDCl\textsubscript{3}), \( \delta \) (ppm): 160.9 (C), 145.7 (2xC), 131.3 (q, \( J = 32.2 \) Hz, 2xC-CF\textsubscript{3}), 123.3 (2xCH), 126.5 (2xCH), 124.1 (q, \( J = 272.5 \) Hz, 2xCF\textsubscript{3}), 120.7 (q, \( J = 4.2 \) Hz, 2xCH), 120.2 (q, \( J = 4.2 \) Hz, 2xCH), 39.5 (2xCH\textsubscript{3}).
2.2. Preparation of alkynes (2)

Alkynes 2a-d and 2h-q were purchased from commercial sources.

Alkynes 2e, S3 2f, S4a 2g S4 and 2r S5 were prepared following literature procedures.

Dodeca-1,11-dien-6-yne (2e)

According to the literature procedure S3, alkyne 2e was synthesized from hept-1-en-6-yne in 50% yield as a transparent oil (100% pentane, Rf 0.95).

$^1$H NMR (300 MHz, CDCl$_3$), $\delta$ (ppm): 5.79 (ddt, $J = 17.0, 10.2, 6.7$ Hz, 2H), 5.1-4.9 (m, 4H), 2.2-2.1 (m, 8H), 1.6-1.5 (m, 4H).

$^{13}$C NMR, DEPT (75 MHz, CDCl$_3$), $\delta$ (ppm): 138.2 (2xCH), 115.0 (2xCH$_2$), 80.2 (2xC), 32.9 (2xCH$_2$), 28.5 (2xCH$_2$), 18.3 (2xCH$_2$).
3. Optimization data

a) Solvent effect

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield 3a (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCE</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>i-PrOH</td>
<td>91</td>
</tr>
<tr>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>CH₃CN</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>1,4-Dioxane</td>
<td>SM</td>
</tr>
<tr>
<td>5</td>
<td>Toluene</td>
<td>SM</td>
</tr>
<tr>
<td>6</td>
<td>t-BuOH</td>
<td>44</td>
</tr>
<tr>
<td>7</td>
<td>t-AmOH</td>
<td>73</td>
</tr>
<tr>
<td>8&lt;sup&gt;c&lt;/sup&gt;</td>
<td>t-AmOH</td>
<td>40</td>
</tr>
<tr>
<td>9&lt;sup&gt;d&lt;/sup&gt;</td>
<td>MeOH</td>
<td>traces</td>
</tr>
<tr>
<td>10</td>
<td>AcOH</td>
<td>SM</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yields. <sup>b</sup>Indole 4a was isolated as minor product (25%).<sup>c</sup>Reaction was carried out under argon atmosphere. <sup>d</sup>Traces of 4a (<3%) was observed by <sup>1</sup>H NMR.
b) Type of catalyst

\[
\begin{align*}
\text{Entry} & \quad \text{Catalyst} & \quad \text{Yield 3a (%)}^a \\
1 & \quad [\text{Cp*RhCl}_2]_2 & \quad 91 \\
2^b & \quad \text{Pd(OAc)}_2 & \quad \text{SM} \\
3 & \quad [\text{Cp*IrCl}_2]_2 & \quad \text{traces} \\
4 & \quad \text{Cp*Rh(OAc)}_2 & \quad 94 \\
5 & \quad - & \quad \text{SM} \\
6 & \quad [\text{Cp*Rh(CH}_3\text{CN)}_3] \text{ (SbF}_6\text{)}_2 & \quad \text{SM} \\
7 & \quad [\text{Rh(COD)}\text{Cl}_2] & \quad \text{SM} \\
8 & \quad [\text{Cp*CoI}_2\text{CO}] & \quad \text{SM} \\
\end{align*}
\]

^aIsolated yields. ^bTraces of benzimidazole (≤5%) were observed by 1H NMR.

c) Temperature

\[
\begin{align*}
\text{Entry} & \quad \text{T (ºC)} & \quad \text{Time (h)} & \quad \text{Yield 3a (%)}^a \\
1 & \quad \text{r.t.} & \quad 17 & \quad 27 \\
2^b & \quad 120 & \quad 3 & \quad \text{Decomposition} \\
3^b & \quad 80\rightarrow95 & \quad 3 & \quad \text{Decomposition} \\
4 & \quad 40 & \quad 16 & \quad 65 \\
5 & \quad 75 & \quad 8 & \quad 84 \\
6 & \quad 60 & \quad 8 & \quad 91 \\
\end{align*}
\]

^aIsolated yields. ^b-t-AmOH as solvent.
d) Additives and oxidants

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive$^a$</th>
<th>Oxidant$^b$</th>
<th>Yield 3a (%)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AgSbF$_6$</td>
<td>Cu(OAc)$_2$.H$_2$O</td>
<td>traces</td>
</tr>
<tr>
<td>2$^d$</td>
<td>Na$_2$CO$_3$</td>
<td>AgOAc/O$_2$</td>
<td>39</td>
</tr>
<tr>
<td>3$^e$</td>
<td>AcOH</td>
<td>Cu(OAc)$_2$</td>
<td>SM</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>Ag(O$_2$CCF$_3$)</td>
<td>Traces</td>
</tr>
<tr>
<td>5</td>
<td>Na$_2$CO$_3$</td>
<td>-</td>
<td>SM</td>
</tr>
<tr>
<td>6</td>
<td>AgCO$_3$</td>
<td>-</td>
<td>SM</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>Ag(OPiv)</td>
<td>51</td>
</tr>
<tr>
<td>8$^f$</td>
<td>-</td>
<td>AgOAc</td>
<td>80</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>AgOAc</td>
<td>91</td>
</tr>
<tr>
<td>10$^g$</td>
<td>Na$_2$CO$_3$</td>
<td>AgOAc</td>
<td>50</td>
</tr>
<tr>
<td>11$^g$</td>
<td>KO'Bu</td>
<td>AgOAc</td>
<td>45</td>
</tr>
<tr>
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<td>AcOH</td>
<td>AgOAc</td>
<td>31</td>
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<tr>
<td>13$^d$</td>
<td>DABCO</td>
<td>AgOAc</td>
<td>78</td>
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</table>

$^a$Additive (13 mol%). $^b$Oxidant (2.1 equiv). $^c$Isolated yields. $^d$AgOAc (25 mol%).
$^e$AcOH (10 mol%) in dioxane. $^f$AgOAc (1.3 equiv). $^g$Additive (10 mol%). $^d$Oxidant (100 mol%).
e) Alkyne loading

\[
\ce{\text{1a}} + \ce{\text{Et=\equiv=Et}} &\xrightarrow{[\text{Cp}^*\text{RhCl}_2\text{]}_2 (2.5 \text{ mol\%})} \ce{\text{AgOAc} (2.1 \text{ eq}) \atop \text{i-PrOH, Air, 8h, 60 °C}} \ce{\text{3a}} \\
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkyne (equiv)</th>
<th>Yield 3a (%)(^a)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>0.8</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>90</td>
</tr>
<tr>
<td>4(^b)</td>
<td>-</td>
<td>SM</td>
</tr>
</tbody>
</table>

\(^a\)Isolated yields. \(^b\)Traces of benzimidazole (<5%) were observed by \(^1\)H NMR.

f) Concentration effect

\[
\ce{\text{1a}} + \ce{\text{Et=\equiv=Et}} &\xrightarrow{[\text{Cp}^*\text{RhCl}_2\text{]}_2 (2.5 \text{ mol\%})} \ce{\text{AgOAc} (2.1 \text{ eq}) \atop \text{i-PrOH, Air, 8h, 60 °C}} \ce{\text{3a}} \\
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Concentration (M)</th>
<th>Yield 3a (%)(^a)</th>
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</thead>
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<td>1</td>
<td>0.037</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>0.2</td>
<td>91</td>
</tr>
</tbody>
</table>

\(^a\)Isolated yields.
g) Alkyne partner

\[
\begin{align*}
\text{Entry} & \quad \text{Alkyne Partner} & \quad \text{Product} & \quad \text{Yield 3 (\%)}^a \\
1 & \quad \text{Et} \equiv \equiv \text{Et} & \quad \text{3a} & \quad 91 \\
2 & \quad \text{n-Pr} \equiv \equiv \text{n-Pr} & \quad \text{3ab} & \quad 70 \\
3 & \quad \text{n-Pr} \equiv \equiv \text{n-Pr} & \quad \text{3fb} & \quad 64 \\
4 & \quad \equiv \equiv \equiv & \quad \text{3ac} & \quad 72 \\
5 & \quad \text{Me} \equiv \equiv \text{Me} & \quad \text{3ad} & \quad 41 \\
6 & \quad \equiv \equiv \equiv & \quad \text{3ae} & \quad 48 \\
\end{align*}
\]
<p>| | | | | |</p>
<table>
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<td><img src="image17" alt="4am" /></td>
<td>traces (b)</td>
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<tr>
<td>15</td>
<td></td>
<td></td>
<td>traces (b)</td>
<td></td>
</tr>
</tbody>
</table>
| #: 16 | \[
\begin{align*}
   &\text{HO} \quad \equiv \quad \equiv \quad \text{OH} \\
   &\text{2o}
\end{align*}
\] | 2n | 4an

| #: 17 | \[
\begin{align*}
   &\text{H} \quad \equiv \quad \equiv \quad \text{n-Pr} \\
   &\text{2p}
\end{align*}
\] | - | -

| #: 18 | \[
\begin{align*}
   &\equiv \quad \equiv \quad \text{Et} \\
   &\text{2q}
\end{align*}
\] | - | -

| #: 19 | \[
\begin{align*}
   &\equiv \quad \equiv \quad \equiv \\
   &\text{2r}
\end{align*}
\] | - | -

\(^{a}\)Isolated yields. \(^{b}\)Traces (GCMS, \(^1\)H NMR), spectroscopic data matched to those in the literature.\(^{\text{S6}}\)
4. General Procedure for the Synthesis of 1,4-Dihydroquinazolin-2-amines (3)

A 25 mL round-bottomed flask was charged with [Cp*RhCl₂]₂ (0.01 mmol, 2.5 mol%), AgOAc (0.84 mmol, 2.1 equiv), i-PrOH (2 mL), guanidine 1 (0.40 mmol, 1.0 equiv), and alkyne 2 (0.40 mmol, 1.0 equiv) under air atmosphere. The mixture was heated at 60 °C for 8 h until disappearance of the starting material (TLC and/or GCMS). The reaction mixture was concentrated and the residue purified by flash column chromatography through alumina Brockmann I neutral using a mixture of Hex/EtOAc with a few drops of i-PrOH as eluent to afford the corresponding 1,4-dihydroquinazoline 3.

\[
\begin{align*}
\text{R}^1 & \quad \text{N} \quad \text{N} \quad \text{R}^2 \\
\text{R}^3 & \quad \text{C} \quad \text{C} \quad \text{R}^4 \\
\end{align*}
\]

\[
\begin{align*}
\text{1} & \quad \text{2} & \quad \text{3} \\
\text{[Cp*RhCl₂]₂ (2.5 mol%)} & \quad \text{AgOAc (2.1 eq)} & \quad \text{i-PrOH, Air, 8h, 60 °C} \\
\end{align*}
\]
5. Data for C4-Disubstituted-1,4-dihydroquinazolin-2-amines (3)

4-Ethyl-N,1-dimethyl-N-phenyl-4-[(1E)-prop-1-en-1-yl]-1,4-dihydroquinazolin-2-amine (3a)

Yellow oil, 91 % yield, (Hex/EtOAc/i-PrOH 0.90:0.099:0.001, $R_f$ 0.82).

$^1$H NMR (500 MHz, CDCl$_3$), $\delta$ (ppm): 7.2-7.1 (m, 4H), 7.0-6.9 (m, 1H), 6.9-6.8 (m, 1H), 6.77 (d, $J = 8.6$ Hz, 2H), 6.59 (d, $J = 7.9$ Hz, 1H), 5.53 (dq, $J = 15.2$, 0.9 Hz, 1H), 5.23 (dq, $J = 15.2$, 6.4 Hz, 1H), 3.28 (s, 3H), 2.79 (s, 3H), 2.0-1.9 (m, 1H), 1.8-1.7 (m, 1H), 1.59 (dd, $J = 6.4$, 0.9 Hz, 3H), 0.87 (t, $J = 7.2$ Hz, 3H).

$^{13}$C NMR, DEPT (126 MHz, CDCl$_3$), $\delta$ (ppm): 151.6 (C), 147.9 (C), 140.7 (C), 137.9 (CH), 129.6 (C), 129.4 (2xCH), 127.0 (CH), 125.7 (CH), 122.8 (CH), 122.6 (CH), 122.2 (CH), 120.2 (2xCH), 112.8 (CH), 61.0 (C), 40.6 (CH$_3$), 33.5 (CH$_3$), 33.2 (CH$_2$), 18.1 (CH$_3$), 8.9 (CH$_3$).

MS, m/z (% relative intensity): 320 [M+H]$^+$, 100), 276 (69).

HRMS (CI) calculated for C$_{21}$H$_{26}$N$_3$ [M+H]$^+$: 320.2121; found: 320.2130.
4-Ethyl-N,1,6-trimethyl-N-(4-methylphenyl)-4-[(1E)-prop-1-en-1-yl]-1,4-dihydroquinazolin-2-amine (3b)

Brown oil, 94% yield, (Hex/EtOAc/i-PrOH 0.90:0.099:0.001, Rf 0.64).

**1H NMR** (400 MHz, CDCl₃), δ (ppm): 7.04 (d, J = 8.2 Hz, 2H), 7.0-6.9 (m, 2H), 6.76 (d, J = 8.2 Hz, 2H), 6.55 (d, J = 8.6 Hz, 1H), 5.61 (d, J = 15.4 Hz, 1H), 5.4-5.3 (m, 1H), 3.31 (s, 3H), 2.84 (s, 3H), 2.34 (s, 3H), 2.28 (s, 3H), 1.98 (dq, J = 14.3, 7.3 Hz, 1H), 1.87 (dq, J = 14.3, 7.3 Hz, 1H), 1.68 (dd, J = 6.5, 1.6 Hz, 3H), 0.96 (t, J = 7.3 Hz, 3H).

**13C NMR, DEPT** (100 MHz, CDCl₃), δ (ppm): 151.7 (C), 145.7 (C), 138.5 (C), 138.0 (CH), 131.8 (C), 131.7 (C), 129.9 (2xCH), 129.8 (C), 127.4 (CH), 126.1 (CH), 122.5 (CH), 120.8 (2xCH), 112.6 (CH), 60.8 (C), 41.0 (CH₃), 33.6 (CH₃), 33.2 (CH₃), 21.1 (CH₃), 20.8 (CH₃), 18.1 (CH₃), 8.9 (CH₃).

**MS**, m/z (% relative intensity): 348 ([M+H]+, 100), 304 (34).

4-Ethyl-6-methoxy-N-(4-methoxyphenyl)-N,1-dimethyl-4-[(1E)-prop-1-en-1-yl]-1,4-dihydroquinazolin-2-amine (3c)

Following the general procedure, the reaction was carried out at 40 °C. Brown oil, 45 % yield, (Hex/EtOAc/i-PrOH 0.85:0.24:0.01, Rf 0.53).

$^{1}$H NMR (400 MHz, CDCl$_3$), δ (ppm): 6.9-6.8 (m, 5H), 6.72 (dd, $J = 8.7$, 2.8 Hz, 1H), 6.54 (d, $J = 8.7$ Hz, 1H), 5.59 (d, $J = 15.4$ Hz, 1H), 5.35 (dq, $J = 15.4$, 6.5 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.27 (s, 3H), 2.80 (s, 3H), 1.95 (dq, $J = 14.6$, 7.3 Hz, 1H), 1.9-1.8 (m, 1H), 1.67 (dd, $J = 6.5$, 1.5 Hz, 3H), 0.96 (t, $J = 7.3$ Hz, 3H).

$^{13}$C NMR, DEPT (100 MHz, CDCl$_3$), δ (ppm): 155.6 (C), 155.4 (C), 152.1 (C), 141.7 (C), 137.7 (CH), 135.0 (C), 131.9 (C), 123.2 (2xCH), 122.7 (CH), 114.7 (2xCH), 113.4 (CH), 111.9 (CH), 111.3 (CH), 60.9 (C), 55.8 (CH$_3$), 55.6 (CH$_3$), 41.7 (CH$_3$), 33.8 (CH$_3$), 33.2 (CH$_2$), 18.1 (CH$_3$), 8.9 (CH$_3$).

MS, m/z (% relative intensity): 380 ([M+H]$^+$, 100), 336 (29).

HRMS (ESI) calculated for C$_{23}$H$_{30}$N$_{3}$O$_2$ [M+H]$^+$: 380.2333; found: 380.2337.
6-Chloro-\(N\)-(4-chlorophenyl)-4-ethyl-N,1-dimethyl-4-[(1E)-prop-1-en-1-yl]-1,4-dihydroquinazolin-2-amine (3d)

Pale yellow oil, 50 % yield, (Hex/i-PrOH 0.999:0.001, \(R_f\) 0.56).

\(^1H\) NMR (400 MHz, CDCl\(_3\)), \(\delta\) (ppm): 7.20 (d, \(J = 8.9\) Hz, 2H), 7.17-6.13 (m, 2H), 6.76 (d, \(J = 8.9\) Hz, 2H), 6.59 (d, \(J = 7.9\) Hz, 1H), 5.57 (d, \(J = 15.3\) Hz, 1H), 5.33 (dq, \(J = 15.3, 6.5\) Hz, 1H), 3.31 (s, 3H), 2.85 (s, 3H), 2.0-1.8 (m, 2H), 1.68 (d, \(J = 6.5\) Hz, 3H), 0.94 (t, \(J = 7.3\) Hz, 3H).

\(^{13}C\) NMR, DEPT (100 MHz, CDCl\(_3\)), \(\delta\) (ppm): 151.1 (C), 146.4 (C), 139.2 (C), 137.1 (CH), 131.4 (C), 129.5 (2xCH), 127.9 (C), 127.5 (C), 127.0 (CH), 125.7 (CH), 123.5 (CH), 121.4 (2xCH), 114.0 (CH), 61.0 (C), 40.7 (CH\(_3\)), 33.6 (CH\(_3\)), 33.2 (CH\(_2\)), 18.0 (CH\(_3\)), 8.8 (CH\(_3\)).

MS, m/z (% relative intensity): 388 ([M+H]^+, 100), 344 (26).

HRMS (CI) calculated for C\(_{21}\)H\(_{24}\)Cl\(_2\)N\(_3\) [M+H]^+: 388.1342; found: 388.1351.
Methyl 4-ethyl-2-[[4-(methoxycarbonyl)phenyl](methyl)amino]-1-methyl-4-[(1E)-prop-1-en-1-yl]-1,4-dihydroquinazoline-6-carboxylate (3e) and methyl[4-cyano(methyl)amino]benzoate (8e)

Compounds 3e and 8e were obtained as an inseparable mixture (5.5:1) in 32 % yield as yellow oil, (Hex/EtOAc/i-PrOH 0.85:0.24:0.01, Rf 0.78).

Spectroscopic data of the major product 3e:

$^1$H NMR (400 MHz, CDCl$_3$), $\delta$ (ppm): 7.92 (dt, $J = 8.9$, 1.5 Hz, 3H), 7.84 (d, $J = 1.9$, 1H), 6.76 (dd, $J = 8.6$, 3.0 Hz, 3H), 5.62 (d, $J = 15.3$ Hz, 1H), 5.3-5.2 (m, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 2.97 (s, 3H), 2.1-2.0 (m, 1H), 1.92 (dq, $J = 14.5$, 7.4 Hz, 1H), 1.67 (d, $J = 6.3$ Hz, 3H), 0.91 (t, $J = 7.3$ Hz, 3H).

$^{13}$C NMR, DEPT (100 MHz, CDCl$_3$), $\delta$ (ppm): 167.1 (CO), 167.0 (CO), 151.0 (C), 150.2 (C), 144.0 (C), 137.4 (CH), 131.4 (3xCH), 129.4 (CH), 128.1 (C), 127.9 (CH), 124.8 (C), 122.5 (C), 116.6 (2xCH), 112.5 (CH), 61.5 (C), 52.1 (CH$_3$), 52.0 (CH$_3$), 39.2 (CH$_3$), 33.7 (CH$_2$), 33.4 (CH$_3$), 18.0 (CH$_3$), 9.0 (CH$_3$).
4-Ethyl-N,1,7-trimethyl-N-(3-methylphenyl)-4-[(1E)-prop-1-en-1-yl]-1,4-dihydroquinazolin-2-amine (3f)

Yellow oil, 79 % yield, (Hex/EtOAc/i-PrOH 0.90:0.099:0.001, Rf 0.81).

$^1$H NMR (400 MHz, CDCl$_3$), δ (ppm): 7.11 (t, $J = 7.8$ Hz, 1H), 7.07 (d, $J = 7.8$ Hz, 1H), 6.88 (d, $J = 7.8$ Hz, 1H), 6.78 (d, $J = 7.6$ Hz, 1H), 6.72 (s, 1H), 6.61 (dd, $J = 8.1$, 1.8 Hz, 1H), 6.48 (s, 1H), 5.61 (d, $J = 15.4$ Hz, 1H), 5.31 (dq, $J = 15.4$, 6.5 Hz, 1H), 3.33 (m, 3H), 2.88 (s, 3H), 2.33 (s, 3H), 2.29 (s, 3H), 1.98 (dq, $J = 13.8$, 7.2 Hz, 1H), 1.87 (dq, $J = 13.8$, 7.2 Hz, 1H), 1.67 (dd, $J = 6.5$ Hz, 3H), 0.94 (t, $J = 7.3$ Hz, 3H).

$^{13}$C NMR, DEPT (100 MHz, CDCl$_3$), δ (ppm): 151.5 (C), 147.9 (C), 140.7 (C), 139.1 (C), 138.2 (CH), 136.7 (C), 129.1 (CH), 126.7 (C), 125.5 (CH), 123.2 (CH), 122.9 (CH), 122.5 (CH), 120.8 (CH), 117.1 (CH), 113.5 (CH), 60.8 (C), 40.5 (CH$_3$), 33.5 (CH$_3$), 33.4 (CH$_2$), 21.7 (CH$_3$), 21.6 (CH$_3$), 18.1 (CH$_3$), 8.9 (CH$_3$).

MS, m/z (% relative intensity): 348 ([M+H]$^+$, 100), 304 (30).

HRMS (ESI) calculated for C$_{23}$H$_{30}$N$_3$ [M+H]$^+$: 348.2434; found: 348.2448.
4-Ethyl-7-methoxy-N-(3-methoxyphenyl)-N,1-dimethyl-4-[(1E)-prop-1-en-1-yl]-1,4-dihydroquinazolin-2-amine (3g)

Pale yellow oil, 42 % yield, (Hex/EtOAc/\(\beta\)-PrOH 0.85:0.24:0.01, \(R_f\) 0.75).

\(^1H\) NMR (400 MHz, CDCl\(_3\)), \(\delta\) (ppm): 7.2-7.1 (m, 1H), 7.07 (d, \(J = 8.5\) Hz, 1H), 6.61 (dd, \(J = 8.5, 2.4\) Hz, 1H), 6.51 (dd, \(J = 8.4, 2.4\) Hz, 1H), 6.44-6.40 (m, 2H), 6.25 (s, 1H), 5.60 (d, \(J = 15.0\) Hz, 1H), 5.3-5.2 (m, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 3.33 (s, 3H), 2.90 (s, 3H), 2.01-1.92 (m, 1H), 1.91-1.83 (m, 1H), 1.66 (dd, \(J = 6.5, 1.5\) Hz, 3H), 0.93 (t, \(J = 7.3\) Hz, 3H).

\(^{13}C\) NMR, DEPT (100 MHz, CDCl\(_3\)), \(\delta\) (ppm): 160.6 (C), 158.9 (C), 151.3 (C), 149.0 (C), 141.7 (C), 138.2 (CH), 130.0 (CH), 126.5 (CH), 122.5 (CH), 121.7 (C), 112.1 (CH), 107.1 (CH), 106.7 (CH), 105.5 (CH), 99.8 (CH), 60.7 (C), 55.4 (CH\(_3\)), 55.2 (CH\(_3\)), 40.2 (CH\(_3\)), 33.41 (CH\(_3\)), 33.39 (CH\(_2\)), 18.0 (CH\(_3\)), 8.9 (CH\(_3\)).

**MS**, m/z (% relative intensity): 380 ([M+H]\(^+\), 100), 336 (31), 218 (16).

**HRMS** (ESI) calculated for C\(_{23}\)H\(_{30}\)N\(_3\)O\(_2\) [M+H]\(^+\): 380.2333; found: 380.2341.
4-Ethyl-\(N,1\)-dimethyl-4-[(\(1E\))-prop-1-en-1-yl]-7-(trifluoromethyl)-\(N\)-[3-(trifluoromethyl)phenyl]-1,4-dihydroquinazolin-2-amine (3h)

Pale yellow oil, 72 % yield, (Hex/EtOAc/i-PrOH 0.95:0.04:0.01, \(R_f\) 0.87).

\(^1\)H NMR (400 MHz, CDCl\(_3\)), \(\delta\) (ppm): 7.27 (t, \(J = 7.9\) Hz, 2H), 7.22-7.18 (m, 1H), 7.14 (d, \(J = 7.9\) Hz, 1H), 7.06 (s, 1H), 6.9-6.8 (m, 2H), 5.52 (dq, \(J = 15.4, 2.0\) Hz, 1H), 5.21 (dq, \(J = 15.4, 6.5\) Hz, 1H), 3.28 (s, 3H), 2.88 (s, 3H), 1.93 (dq, \(J = 14.4, 7.3\) Hz, 1H), 1.82 (dq, \(J = 14.4, 7.3\) Hz, 1H), 1.60 (dd, \(J = 6.5, 2.0\) Hz, 3H), 0.85 (t, \(J = 7.3\) Hz, 3H).

\(^{13}\)C NMR, DEPT (100 MHz, CDCl\(_3\)), \(\delta\) (ppm): 150.8 (C), 147.9 (C), 140.8 (C), 137.1 (CH), 132.8 (C), 132.0 (q, \(J = 32.2\) Hz, C-CF\(_3\)), 130.0 (CH), 129.7 (q, \(J = 32.2\) Hz, C-CF\(_3\)), 126.4 (CH), 124.3 (q, \(J = 272.1\) Hz, CF\(_3\)), 124.1 (q, \(J = 272.4\) Hz, CF\(_3\)), 124.0 (CH), 121.9 (CH), 119.8 (q, \(J = 3.9\) Hz, CH), 118.5 (q, \(J = 3.8\) Hz, CH), 115.9 (q, \(J = 3.8\) Hz, CH), 109.6 (q, \(J = 3.9\) Hz, CH), 61.4 (C), 39.9 (CH\(_3\)), 33.5 (CH\(_3\)), 33.4 (CH\(_2\)), 18.0 (CH\(_3\)), 8.8 (CH\(_3\)).

MS, m/z (% relative intensity): 456 ([M+H]\(^+\), 100).

HRMS (ESI) calculated for C\(_{23}\)H\(_{24}\)F\(_6\)N\(_3\) [M+H]\(^+\): 456.1869; found: 456.1869.
4-[(1E)-but-1-en-yl]-N,1-dimethyl-N-phenyl-4-propyl-1,4-dihydroquinazolin-2-amine (3ab)

Yellow oil, 70 % yield, (Hex/EtOAc/i-PrOH 0.90:0.099:0.001, Rf 0.81).

$^1$H NMR (400 MHz, CDCl$_3$), δ (ppm): 7.2-7.1 (m, 2H), 7.1-7.0 (m, 2H), 6.98 (td, $J = 7.4, 1.2$ Hz, 1H), 6.88 (t, $J = 7.4$ Hz, 1H), 6.8-6.7 (m, 2H), 6.59 (dd, $J = 8.4, 1.2$ Hz, 1H), 5.49 (dt, $J = 15.3, 1.5$ Hz, 1H), 5.25 (dt, $J = 15.3, 6.3$ Hz, 1H), 5.27 (s, 3H), 2.79 (s, 3H), 2.0-1.9 (m, 2H), 1.9-1.8 (m, 1H), 1.8-1.7 (s, 1H), 1.4-1.3 (m, 2H), 0.9-0.8 (m, 6H).

$^{13}$C NMR, DEPT (100 MHz, CDCl$_3$), δ (ppm): 151.4 (C), 147.9 (C), 140.6 (C), 135.8 (CH), 130.1 (C), 129.6 (CH), 129.4 (2xCH), 127.0 (CH), 125.5 (CH), 122.6 (CH), 122.1 (CH), 120.1 (2xCH), 112.8 (CH), 60.7 (C), 43.2 (CH$_2$), 40.5 (CH$_3$), 33.5 (CH$_3$), 25.5 (CH$_2$), 17.7 (CH$_2$), 14.8 (CH$_3$), 14.0 (CH$_3$).

MS, m/z (% relative intensity): 348 (M, 93), 304 (100).

HRMS (CI) calculated for C$_{23}$H$_{30}$N$_3$: 348.2440; found: 348.2447.
4-[(1E)-But-1-en-1-yl]-N,1,7-trimethyl-N-(3-methylphenyl)-4-propyl-1,4-dihydroquinazolin-2-amine (3fb)

Yellow oil, 64 % yield, (Hex/EtOAc/i-PrOH 0.90:0.099:0.001, Rf 0.68).

\textbf{1H NMR} (400 MHz, CDCl$_3$), $\delta$ (ppm): 7.1-7.0 (m, 2H), 6.88 (dd, $J = 7.6$, 1.7 Hz, 1H), 6.78 (d, $J = 7.6$ Hz, 1H), 6.72 (s, 1H). 6.62 (d, $J = 8.7$ Hz, 1H), 6.49 (s, 1H), 5.58 (d, $J = 15.3$ Hz, 1H), 5.34 (dt, $J = 15.3$, 6.3 Hz, 1H), 3.33 (s, 3H), 2.88 (s, 3H), 2.34 (s, 3H), 2.30 (s, 3H), 2.1-2.0 (m, 2H), 2.0-1.9 (m, 1H), 1.9-1.8 (m, 1H), 1.5-1.4 (m, 2H), 1.0-0.9 (m, 6H).

\textbf{13C NMR, DEPT} (100 MHz, CDCl$_3$), $\delta$ (ppm): 151.4 (C), 147.9 (C), 140.6 (C), 139.1 (C), 136.6 (C), 136.1 (CH), 129.3 (CH), 129.1 (CH), 127.2 (C), 125.4 (CH), 123.2 (CH), 122.8 (CH), 120.6 (CH), 117.0 (CH), 113.5 (CH), 60.5 (C), 43.5 (CH$_2$), 40.4 (CH$_3$), 33.5 (CH$_3$), 25.5 (CH$_2$), 21.7 (CH$_3$), 21.5 (CH$_3$), 17.7 (CH$_2$), 14.8 (CH$_3$), 14.0 (CH$_3$).

\textbf{MS}, m/z (% relative intensity): 376 ([M+H]$^+$, 100), 318 (23), 158 (25).

\textbf{HRMS} (ESI) calculated for C$_{25}$H$_{34}$N$_3$ [M+H]$^+$: 376.2747; found: 376.2754.
4-Butyl-N,1-dimethyl-4-[(1E)-pent-1-en-1-yl]-N-phenyl-1,4-dihydroquinazolin-2-amine (3ac)

Pale yellow oil, 72 % yield, (Hex/EtOAc/i-PrOH 0.90:0.099:0.001, Rf 0.67).

$^1$H NMR (300 MHz, CDCl$_3$), δ (ppm): 7.2-7.1 (m, 4H), 7.0-6.9 (m, 1H), 6.9-6.8 (m, 1H), 6.76 (d, $J = 7.5$ Hz, 2H), 6.59 (d, $J = 7.5$ Hz, 1H), 5.48 (d, $J = 15.4$ Hz, 1H), 5.16 (dt, $J = 15.4$, 6.8 Hz, 1H), 3.27 (s, 3H), 2.79 (m, 3H), 1.9-1.8 (m, 3H), 1.8-1.7 (m, 1H), 1.4-1.2 (m, 6H), 0.9-0.7 (m, 6H).

$^{13}$C NMR, DEPT (75 MHz, CDCl$_3$), δ (ppm): 151.4 (C), 147.9 (C), 140.7 (C), 136.9 (CH), 130.2 (C), 129.4 (2xCH), 127.8 (CH), 126.9 (CH), 125.5 (CH), 122.6 (CH), 122.0 (CH), 120.0 (2xCH), 112.7 (CH), 60.8 (C), 40.5 (CH$_3$), 40.4 (CH$_2$), 34.6 (CH$_2$), 33.4 (CH$_3$), 26.7 (CH$_2$), 23.5 (CH$_2$), 22.8 (CH$_2$), 14.4 (CH$_3$), 13.7 (CH$_3$).

MS, m/z (% relative intensity): 376 ([M+H]$^+$, 100), 318 (63).

HRMS (CI) calculated for C$_{25}$H$_{34}$N$_3$ [M+H]$^+$: 376.2753; found: 376.2755.
Following the general procedure, the reaction was carried out in a sealed tube at 40 °C. Yellow oil, 41 % yield, (Hex/EtOAc/i-PrOH 0.90:0.099:0.001, Rf 0.45).

\(^1\)H NMR (400 MHz, CDCl\(_3\)), δ (ppm): 7.2-7.1 (m, 4H), 7.03 (td, J = 7.4, 1.2 Hz, 1H), 6.90 (t, J = 7.4 Hz, 1H), 6.76 (d, J = 8.4 Hz, 2H), 6.63 (d, J = 7.8 Hz, 1H), 5.91 (dd, J = 17.2, 10.2 Hz, 1H), 4.91 (d, J = 10.2 Hz, 1H), 4.70 (d, J = 17.2, 1H), 3.31 (s, 3H), 2.80 (s, 3H), 1.62 (s, 3H).

\(^{13}\)C NMR, DEPT (100 MHz, CDCl\(_3\)), δ (ppm): 152.5 (C), 147.5 (C), 144.8 (CH), 140.3 (C), 130.7 (C), 129.4 (2xCH), 127.4 (CH), 124.9 (CH), 123.1 (CH), 122.4 (CH), 120.5 (2xCH), 112.9 (CH), 111.1 (CH\(_2\)), 58.6 (C), 40.7 (CH\(_3\)), 33.6 (CH\(_3\)), 27.4 (CH\(_3\)).

MS, m/z (% relative intensity): 292 ([M+H]\(^+\), 100), 262 (32), 185 (11).

HRMS (ESI) calculated for C\(_{19}\)H\(_{22}\)N\(_3\) [M+H]\(^+\): 292.1808; found: 292.1810.
4-[(1E)-hexa-1,5-dien-1-yl]-N,N1-dimethyl-4-pent-4-en-1-yl-N-phenyl-1,4-dihydroquinazolin-2-amine (3ae)

Yellow oil, 48 % yield, (Hex/EtOAc/i-PrOH 0.95:0.049:0.001, $R_f$ 0.71).

$^1$H NMR (400 MHz, CDCl$_3$), δ (ppm): 7.3-7.1 (m, 4H), 7.04 (t, $J = 7.2$ Hz, 1H), 6.94 (t, $J = 7.2$ Hz, 1H), 6.82 (d, $J = 7.7$ Hz, 2H), 6.64 (d, $J = 7.7$ Hz, 1H), 5.9-5.7 (m, 2H), 5.55 (d, $J = 15.3$ Hz, 1H), 5.25 (dt, $J = 15.3$, 6.1 Hz, 1H), 5.0-4.9 (m, 2H), 4.9-4.8 (m, 2H), 3.32 (s, 3H), 2.84 (s, 3H), 2.1-2.0 (m, 6H), 1.96 (ddd, $J = 13.2$, 11.1, 5.4 Hz, 1H), 1.85 (ddd, $J = 13.2$, 11.5, 5.4 Hz, 1H), 1.6-1.5 (m, 2H).

$^{13}$C NMR, DEPT (100 MHz, CDCl$_3$), δ (ppm): 151.5 (C), 147.9 (C), 140.7 (C), 139.5 (CH), 138.6 (CH), 137.1 (CH), 129.9 (C), 129.4 (2xCH), 127.2 (CH), 127.0 (CH), 125.4 (CH), 122.6 (CH), 122.2 (CH), 120.2 (2xCH), 114.6 (CH$_2$), 114.3 (CH$_2$), 112.8 (CH), 60.7 (C), 40.6 (CH$_3$), 40.0 (CH$_2$), 34.5 (CH$_2$), 33.9 (CH$_2$), 33.5 (CH$_3$), 31.9 (CH$_2$), 23.8 (CH$_2$).

MS, m/z (% relative intensity): 400 ([M+H]$^+$, 100), 316 (10).

HRMS (ESI) calculated for C$_{27}$H$_{34}$N$_3$ [M+H]$^+$: 400.2747; found: 400.2752.
4-Butyl-N,1-dimethyl-4-[(1E)-3-methylbuta-1,3-dien-1-yl]-N-phenyl-1,4-dihydroquinazolin-2-amine (3af)

Yellow oil, 76 % yield, (Hex/EtOAc/i-PrOH 0.90:0.099:0.001, Rf 0.67).

**$^1$H NMR** (300 MHz, CDCl$_3$), δ (ppm): 7.3-7.2 (m, 4H), 7.1-7.0 (m, 1H), 6.97 (t, $J = 7.3$ Hz, 1H), 6.86 (t, $J = 7.8$ Hz, 2H), 6.68 (d, $J = 7.8$ Hz, 1H), 6.01 (d, $J = 15.7$ Hz, 1H), 5.82 (d, $J = 15.7$ Hz, 1H), 4.87 (d, $J = 6.9$ Hz, 2H), 3.36 (s, 3H), 2.87 (s, 3H), 2.1-1.9 (m, 1H), 1.9-1.8 (m, 1H), 1.84 (s, 3H), 1.4-1.3 (m, 4H), 0.90 (t, $J = 6.9$ Hz, 3H).

**$^{13}$C NMR, DEPT** (75 MHz, CDCl$_3$), δ (ppm): 151.5 (C), 147.9 (C), 142.3 (C), 140.6 (C), 137.2 (CH), 130.3 (CH), 129.8 (C), 129.4 (2xCH), 127.1 (CH), 125.6 (CH), 122.7 (CH), 122.2 (CH), 120.2 (2xCH), 115.5 (CH$_2$), 112.9 (CH), 60.8 (C), 40.9 (CH$_2$), 40.6 (CH$_3$), 33.5 (CH$_3$), 26.7 (CH$_2$), 23.4 (CH$_2$), 19.1 (CH$_3$), 14.4 (CH$_3$).

**MS**, m/z (% relative intensity): 374 ([M+H]$^+$, 100), 316 (48).

**HRMS** (CI) calculated for C$_{25}$H$_{32}$N$_3$ [M+H]$^+$: 374.2596; found: 374.2597.
4-(2-{{[tert-butyl(dimethyl)silyl]oxy}ethyl})-N,1-dimethyl-4-[(1E)-3-methylbuta-1,3-dien-1-yl]-N-phenyl-1,4-dihydroquinazolin-2-amine (3ag)

Pale yellow oil, 62 % yield, (Hex/EtOAc/i-PrOH 0.90:0.099:0.001, Rf 0.72).

$^1$H NMR (400 MHz, CDCl$_3$), δ (ppm): 7.3-7.2 (m, 4H), 7.09 (td, $J = 7.3$, 1.2 Hz, 1H), 7.02 (t, $J = 7.3$ Hz, 1H), 6.89 (d, $J = 7.3$ Hz, 2H), 6.67 (d, $J = 6.7$ Hz, 1H), 6.05 (d, $J = 15.7$ Hz, 1H), 5.84 (d, $J = 15.7$ Hz, 1H), 4.90 (d, $J = 8.5$ Hz, 2H), 3.9-3.8 (m, 2H), 3.35 (s, 3H), 2.87 (s, 3H), 2.34 (ddd, $J = 13.0$, 9.2, 6.3 Hz, 1H), 2.19 (ddd, $J = 13.0$, 9.2, 6.3 Hz, 1H), 1.86 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H).

$^{13}$C NMR, DEPT (100 MHz, CDCl$_3$), δ (ppm): 151.6 (C), 148.1 (C), 142.1 (C), 140.4 (C), 136.2 (CH), 130.5 (CH), 129.5 (2xCH), 129.4 (C), 127.3 (CH), 125.4 (CH), 122.8 (CH), 122.7 (CH), 121.1 (2xCH), 115.7 (CH$_2$), 112.9 (CH), 60.5 (CH$_2$), 59.6 (C), 43.4 (CH$_2$), 41.1 (CH$_3$), 33.6 (CH$_3$), 29.2 (3xCH$_3$), 19.0 (CH$_3$), 18.5 (C), -5.0 (2xCH$_3$).

MS, m/z (% relative intensity): 476 ([M+H]$^+$, 100).

HRMS (ESI) calculated for C$_{29}$H$_{42}$N$_3$OSi [M+H]$^+$: 476.3092; found: 476.3093.
1’-Methyl-2’-[methyl(phenyl)amino]-1’H-spiro[furan-3,4’-quinazolin]-5(4H)-one

(3ah)

Following the general procedure, but the reaction residue was purified by flash column chromatography through activated alumina (Brockmann V grade). Brown oil, 68 % yield, (DCM, Rf 0.65).

\(^1\)H NMR (400 MHz, CDCl\(_3\)), \(\delta\) (ppm): 7.33-7.27 (m, 2H), 7.26-7.22 (m, 2H), 7.14 (dt, \(J = 7.5, 1.1\) Hz, 1H), 7.04 (t, \(J = 7.5\) Hz, 1H), 6.83 (dd, \(J = 7.2, 1.3\) Hz, 2H), 6.75 (dd, \(J = 8.1, 1.1\) Hz, 1H), 4.55 (d, \(J = 8.9\) Hz, 1H), 4.46 (d, \(J = 8.9\) Hz, 1H), 3.31 (s, 3H), 2.87 (s, 3H), 2.86 (s, 2H).

\(^{13}\)C NMR, DEPT (100 MHz, CDCl\(_3\)), \(\delta\) (ppm): 175.9 (CO), 153.8 (C), 147.1 (C), 140.1 (C), 129.6 (2xCH), 128.6 (CH), 126.9 (C), 123.8 (CH), 123.7 (CH), 123.1 (CH), 121.7 (2xCH), 113.5 (CH), 79.1 (CH\(_2\)), 61.2 (C), 43.5 (CH\(_2\)), 41.4 (CH\(_3\)), 34.0 (CH\(_3\)).

MS, m/z (% relative intensity): 322 ([M+H]^+) 62), 280 (100).

HRMS (ESI) calculated for C\(_{19}\)H\(_{20}\)N\(_{3}\)O\(_{2}\) [M+H]^+: 322.1550; found: 322.1561.
1',2,5-trimethyl-2'-[methyl(phenyl)amino]-4,5-dihydro-1'H-spiro[furan-3,4'-quinazolin]-5-ol (3ai)

Following the general procedure, but the reaction residue was purified by flash column chromatography through activated alumina (Brockmann V grade). Pale yellow oil as an inseparable diastereoisomer mixture 8.5:1 in 65% yield, (100% DCM, Rf 0.60).

Spectroscopic data of major product (3ai):

**1H NMR** (400 MHz, CDCl₃), δ (ppm): 7.3-7.2 (m, 3H), 7.15 (dd, J = 7.4, 1.6 Hz, 1H), 7.08 (td, J = 7.6, 1.1 Hz, 1H), 7.03 (ddt, J = 8.7, 7.3, 1.1 Hz, 1H), 6.83 (d, J = 7.3 Hz, 2H), 6.67 (d, J = 7.6 Hz, 1H), 4.25 (q, J = 6.5 Hz, 1H), 3.25 (s, 3H), 2.81 (s, 3H), 2.67 (d, J = 12.1 Hz, 1H), 2.25 (d, J = 12.1 Hz, 1H), 1.62 (s, 3H), 0.58 (d, J = 6.5 Hz, 3H).

**13C NMR, DEPT** (100 MHz, CDCl₃), δ (ppm): 152.6 (C), 147.1 (C), 140.4 (C), 129.6 (2xCH), 128.1 (CH), 125.7 (C), 124.4 (CH), 124.0 (CH), 123.2 (CH), 122.3 (2xCH), 113.1 (CH), 104.6 (C), 85.3 (CH), 68.0 (C), 44.4 (CH₂), 41.6 (CH₃), 33.8 (CH₃), 26.9 (CH₃), 20.3 (CH₃).

**MS**, m/z (% relative intensity): 352 ([M+H]⁺, 30), 334 (66), 294 (100).

6. Data for Indoles 4a and 4e

2,3-Diethyl-1-methyl-1H-indole (4a)

Follow the general procedure using CH₃CN as solvent. Pale yellow oil, 25 % yield, (Hex/EtOAc 0.90:0.10, Rᵣ 0.88).

¹H NMR (400 MHz, CDCl₃), δ (ppm): 7.55 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.16 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H), 7.07 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H), 3.68 (s, 3H), 2.8-2.7 (m, 4H), 1.3-1.2 (s, 6H).

¹³C NMR, DEPT (100 MHz, CDCl₃), δ (ppm): 138.1 (C), 136.8 (C), 127.6 (C), 120.6 (CH), 118.7 (CH), 118.3 (CH), 112.8 (C), 108.7 (CH), 29.5 (CH₃), 17.8 (2xCH₂), 16.4 (CH₃), 15.1 (CH₃).

Methyl 2,3-diethyl-1-methyl-1H-indole-5-carboxylate (4e)

Follow the general procedure using CH₃CN as solvent. Pale yellow oil, 19 % yield, (Hex/EtOAc/i-PrOH 0.85:0.024:0.001, Rᵣ 0.95).

¹H NMR (400 MHz, CDCl₃), δ (ppm): 8.30 (s, 1H), 7.86 (dd, J = 8.6 Hz, 1H), 7.24 (d, J = 8.6 Hz, 1H), 3.93 (s, 3H), 3.70 (s, 3H), 2.77 (p, J = 7.7 Hz, 4H), 1.3-1.2 (s, 6H).

¹³C NMR, DEPT (100 MHz, CDCl₃), δ (ppm): 168.7 (CO), 139.5 (C), 139.4 (C), 127.3 (C), 122.3 (CH), 121.3 (CH), 120.6 (C), 114.5 (C), 108.3 (CH), 51.9 (CH₃), 29.6 (CH₃), 17.9 (CH₂), 17.6 (CH₂), 16.5 (CH₃), 14.9 (CH₃).

MS, m/z (% relative intensity): 246 ([M+H]^⁺, 13), 202 (100), 172 (88).

7. Mechanistic experiments

7.1. Experimental Procedure and Spectroscopic Data of Complexes 5 and 6

Preparation of rhodacycle 5a

A 25 mL Schlenk tube was charged with [Cp*RhCl2]2 (50.0 mg, 0.081 mmol), NaOAc (40.0 mg, 0.486 mmol) and N,N’-dimethyl-N,N’-diphenylguanidine (1a) (43.0 mg, 0.18 mmol) in methanol (5 ml). The reaction mixture was stirred at room temperature for 2 h and then solvents were removed under vacuum. The residue was purified by flash column chromatography through alumina Brockmann I neutral (DCM) affording complex 5a as a yellow microcrystalline solid (67.0 mg, 81%). The crystals used in the X-ray study were grown by slow diffusion of layers of diethylether and petroleum ether into a dichloromethane solution of the complex at 273 K.

\(^1\text{H NMR}\) (300 MHz, CD2Cl2), \(\delta\) (ppm): 7.57 (m, 1H), 7.34 (m, 2H), 7.15 (m, 1H), 6.98 (m, 2H), 6.91 (m, 2H), 6.53 (m, 1H), 5.41 (bs, 1H, NH), 3.42, 2.84 (2s, 2x3H, NMe), 1.54 (s, 15H, Cp*).

\(^{13}\text{C NMR}\) (75 MHz, CD2Cl2), \(\delta\) (ppm): 159.8 (s, C=NH), 155.6 (d, \(J_{Rh-C} = 31.4\) Hz, C-Rh), 145.6, 145.4 (2s, 2xC\(^1\)-N), 140.5 (d, \(J_{Rh-C} = 2.7\) Hz, CH), 130.0 (s, 2xCH), 125.0 (s, CH), 124.7 (s, CH), 123.2 (s, 2xCH), 123.1 (s, CH), 115.9 (s, CH), 95.0 (d, \(J_{Rh-C} = 6.5\) Hz, Cp*), 40.3, 38.4 (2s, 2xNMe), 9.2 (s, Cp*).

\textbf{Anal} calculated for C\(_{25}\)H\(_{31}\)ClN\(_3\)Rh: C, 58.66, H, 6.10, N, 8.21; found: C, 58.27, H, 6.69, N, 8.00.
Preparation of rhodacycle 5b

Method A: A mixture of [Cp*Rh(OAc)2] (50.0 mg, 0.140 mmol) and N,N'-dimethyl-N,N'-diphenylguanidine (1a) (43.0 mg, 0.18 mmol) was stirred at room temperature in dichloromethane (5 mL) for 2 h. The mixture was then filtered through Celite and evaporated to dryness. The reaction crude was washed with petroleum ether (3 x 2 mL) to remove excess of 1a. Cyclometalated complex 5b was isolated as a yellow microcrystalline solid (67.0 mg, 90%). Further purification of this compound could be achieved through chromatography on silica with a significant decrease in yield.

Method B: Silver acetate (16.7 mg, 0.100 mmol) was added to a solution of complex 5a (51.1 mg, 0.100 mmol) in 5 mL of dichloromethane and the mixture was stirred for 30 min. The solution was then filtered via cannula. Removal of solvent from the filtrate gave complex 5b as a pale yellow microcrystalline solid (51 mg, 95%).

1H NMR (300 MHz, CD2Cl2), δ (ppm): 7.72 (dd, J = 6.6, 2.4 Hz, 1H), 7.43 (bs, 1H, NH), 7.33 (t, J = 7.7 Hz, 2H), 7.13 (t, J = 7.4 Hz, 1H), 7.01-6.88 (m, 4H), 6.54 (dd, J = 7.0, 2.2 Hz, 1H), 3.46, 2.79 (2s, 2x3H, NMe), 1.88 (s, 3H, OAc), 1.53 (s, 15H, Cp*).

13C NMR (75 MHz, CD2Cl2), δ (ppm): 178.5 (s, OAc), 158.5 (s, C=NH), 157.5 (d, JRh-C = 32.1 Hz, C-Rh), 146.2, 145.8 (2s, 2xC1-N), 138.4 (d, JRh-C = 2.8 Hz, CH), 139.9 (s, 2xCCH), 124.7 (s, CH), 124.6 (s, CH), 123.2 (s, CH), 123.0 (s, 2xCCH), 116.0 (s, CH), 93.8 (d, JRh-C = 6.3 Hz, Cp*), 40.4, 37.9 (2s, 2xNMe), 25.7 (s, 3H, OAc), 9.1 (s, Cp*).
Preparation of rhodacycle 6a

3-Hexyne (14 μL, 0.120 mmol) was added to a solution of complex 5a (51.1 mg, 0.100 mmol) in methanol (2 mL), upon which the mixture changed instantaneously from orange to dark red. The solvent was then removed under vacuum and the residue was solved in dichloromethane and filtered through Celite. After solvents removal under vacuum, complex 6a was obtained as a brown microcrystalline solid (55.0 mg, 93%). The crystals used in the X-ray study were grown by slow diffusion of layers of diethylether and petroleum ether into a dichloromethane solution of the complex at 273 K.

$^1$H NMR (300 MHz, CD$_3$OD), δ (ppm): 7.75 (ddd, $J = 8.1, 7.0, 1.4$ Hz, 1H), 7.63 (ddd, $J = 8.6, 7.0, 1.7$ Hz, 1H), 7.51-7.39 (m, 2H), 7.31 (ddd, $J = 9.5, 8.0, 1.4$ Hz, 2H), 7.22-7.01 (m, 3H), 3.37, 2.53 (2s, 2x3H, NMe), 2.93 (dq, $J = 14.8, 7.4$ Hz, 1H, CH$_2$), 2.58 (dq, $J = 15.1, 7.5$ Hz, 1H, CH$_2$), 2.44 (dq, $J = 15.3, 7.5$ Hz, 1H, CH$_2$), 2.22 (dq, $J = 14.8, 7.5$ Hz, 1H, CH$_2$), 1.32 (s, 15H, Cp*), 1.16, 0.92 (2t, $J = 7.6, 7.6$ Hz, 2x3H, CH$_3$).

$^{13}$C NMR (75 MHz, CD$_2$Cl$_2$), δ (ppm): 168.4 (bs, C-Rh), 166.8 (s, C=NH), 146.4 (s, C$^1$-N), 140.9 (bs, C$^1$-N), 131.9 (bs, C), 131.7 (bs, C), 129.9 (s, CH), 129.8 (s, 2xCH), 128.4 (s, CH), 127.4 (s, CH), 126.5 (s, CH), 124.0 (s, CH), 122.1 (s, 2xCH), 95.3 (d, $J_{Rh-C} = 6.6$ Hz, Cp*), 40.6, 40.4 (2s, 2xNMe), 33.7 (bs, CH$_2$), 28.2 (s, CH$_2$), 15.6, 15.4 (2s, 2xCH$_3$), 8.8 (s, Cp*).

Anal calculated for C$_{31}$H$_{41}$ClN$_3$Rh: C, 62.68, H, 6.96, N, 7.07; found: C, 62.41, H, 7.09, N, 6.79.
Preparation of rhodacyle 6b

Method A: 3-Hexyne (14 μL, 0.120 mmol) was added to a solution of complex 5b (53.5 mg, 0.100 mmol) in methanol (2 mL), upon which the color mixture changed instantaneously from orange to brown. Removal of the solvent gave a brown residue containing 6b as the major component.

Method B: Silver acetate (16.7 mg, 0.100 mmol) was added to a solution of complex 6a (59.3 mg, 0.100 mmol) in dichloromethane (5 mL) and the mixture was stirred for 15 min. The solution was then filtered with a cannula. Removal of solvent from the filtrate gave complex 6b as a brown solid (56.3 mg, 91%).

$^1$H NMR (300 MHz, CD$_3$OD), δ (ppm): 7.75 (ddd, $J = 8.2, 7.0, 1.3$ Hz, 1H), 7.63 (ddd, $J = 8.6, 7.0, 1.7$ Hz, 1H), 7.51 – 7.40 (m, 2H), 7.31 (ddd, $J = 9.8, 8.1, 1.5$ Hz, 2H), 7.17 – 7.05 (m, 3H), 3.37, 2.52 (2s, 2x3H, NMe), 2.93 (dq, $J = 14.8, 7.4$ Hz, 1H, CH$_2$), 2.58 (dq, $J = 15.1, 7.6$ Hz, 1H, CH$_2$), 2.43 (dq, $J = 15.2, 7.8$ Hz, 1H, CH$_2$), 2.22 (dq, $J = 14.9, 7.6$ Hz, 1H, CH$_2$), 1.90 (s, 3H, OAc), 1.32 (s, 15H, Cp*), 1.14, 0.92 (2t, $J = 7.6, 7.6$ Hz, 2x3H, CH$_3$).
7.2. X-Ray Crystallographic Data

The X-Ray intensity data were collected on a Bruker X8 Apex-II CCD diffractometer using graphite-monochromated MoKα radiation (λ = 0.71073 Å) at 100 K. The software APEX-II was used for collecting frames with omega/phi scans measurement method. The SORTAV software was used for the data reduction, and a multi-scan absorption correction was applied with SADABS2014. SHELXT-2014 program was used to solve the structure and refinement was performed by full-matrix least squares on $F^2$ with SHELXL2014. During the solution process, complex 5a was found to crystallize with two molecules of dichloromethane. On the other hand, in complex 6a, one of the NMe groups and a terminal methyl group of the 3-hexyne chain were found to be disordered in two positions. In addition, the hydrogen atom of nitrogen linked to Rh does not appear clearly in the electron density map. It has been placed in this position and refined given geometric constraints.

![X-Ray structure (ellipsoids at 30% probability) of complex 5a.](image)

Table 1. Crystal data and structure refinement for complex 5a.
Identification code  shelx
Empirical formula  C_{25}H_{31}ClN_{3}Rh, 2(CH_{2}Cl_{2})
Formula weight  681.74
Temperature  100(2) K
Wavelength  0.71073 Å
Crystal system  Triclinic
Space group  P\textsuperscript{\textprime}-1
Unit cell dimensions  
\begin{align*}
a &= 11.1440(2) \text{ Å} \\
b &= 11.7173(2) \text{ Å} \\
c &= 13.5405(2) \text{ Å} \\
\alpha &= 80.6465(11)° \\
\beta &= 68.8848(10)° \\
\gamma &= 63.5599(10)°
\end{align*}
Volume  1476.85(5) Å\textsuperscript{3}
Z  2
Density (calculated)  1.533 Mg/m\textsuperscript{3}
Absorption coefficient  1.052 mm\textsuperscript{-1}
F(000)  696
Crystal size  0.390 x 0.230 x 0.200 mm\textsuperscript{3}
Theta range for data collection  1.612 to 31.611°
Index ranges  -16<=h<=16, -17<=k<=17, -19<=l<=19
Reflections collected  58363
Independent reflections  9859 [R(int) = 0.0583]
Completeness to theta = 25.242°  99.8 %
Refinement method  Full-matrix least-squares on F\textsuperscript{2}
Data / restraints / parameters  9859 / 0 / 336
Goodness-of-fit on F\textsuperscript{2}  1.057
Final R indices [I>2sigma(I)]  R1 = 0.0344, wR2 = 0.0646
R indices (all data)  R1 = 0.0466, wR2 = 0.0686
Largest diff. peak and hole  0.856 and -0.790 e.Å\textsuperscript{-3}
Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for complex 5a. U(eq) is defined as one third of the trace of the orthogonalized U_ij tensor.

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X-Ray structure (ellipsoids at 30% probability) of complex 6a.

Table 3. Crystal data and structure refinement for complex 6a.

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<td>Density (calculated)</td>
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Absorption coefficient 0.725 mm$^{-1}$

F(000) 1240

Crystal size 0.500 x 0.040 x 0.030 mm$^3$

Theta range for data collection 1.323 to 26.413°

Index ranges -19<=$h$<=$19$, -13<=$k$<=$13$, -20<=$l$<=$20$

Reflections collected 39042

Independent reflections 5770 [R(int) = 0.1368]

Completeness to theta = 25.242° 100.0 %

Refinement method Full-matrix least-squares on F$^2$

Data / restraints / parameters 5770 / 366 / 356

Goodness-of-fit on F$^2$ 1.050

Final R indices [I$>$2sigma(I)] R1 = 0.0726, wR2 = 0.1123

R indices (all data) R1 = 0.1292, wR2 = 0.1294

Largest diff. peak and hole 0.821 and -1.175 e.Å$^{-3}$

Table 4. Atomic coordinates (x 10$^4$) and equivalent isotropic displacement parameters (Å$^2$x 10$^3$) for complex 6a. U(eq) is defined as one third of the trace of the orthogonalized U$ij$ tensor.

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7.3. Deuterium Experiments

Guanidine 1a and 3-hexyne (2a) were subjected to the standard cyclization reaction conditions employing AcOD as solvent. After complete consumption of guanidine, solvents were evaporated to dryness followed by flash column chromatography isolating the 1,4-dihydroquinazolin-2-amine 3a-d in 70% yield (66% D).
To a solution of rhodacycle 6b in \textit{i}PrOH was added acetic acid at room temperature. After 1 hour, the reaction was monitored by $^1$H NMR affording quinazoline 3a (major compound) and styrene derivative 7a (minor compound).
References


8. Spectra