Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201500680

One-Pot Olefin Isomerization/Aliphatic Enamine Ring-Closing Metathesis/Oxidation/1,3-Dipolar Cycloaddition for the Synthesis of Isoindolo[1,2-*a*]isoquinolines

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Received: July 17, 2015; Revised: August 22, 2015; Published online: December 9, 2015

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201500680.

Abstract: *N*-Alkyl-*N*-(2-vinylbenzyl)prop-2-en-1-amine derivatives undergo a one-pot olefin isomerization/aliphatic enamine ring-closing metathesis (RCM)/oxidation/1,3-dipolar cycloaddition sequence with the ruthenium complex, $Ru(CO)HCl(PPh_3)_3$, a second generation Hoveyda–Grubbs catalyst, and a 1,3-dipolarophile. Overall, in a single operation the reaction sequence converts simple benzylamine derivatives into isoindolo[1,2-*a*]isoquinolines with a π-conjugated four-ring system, through three unique ruthenium-catalyzed transformations.

Keywords: cycloaddition; domino reactions; heterocycles; metathesis; ruthenium

Olefin metathesis using ruthenium carbene catalysts (Figure 1) is one of the most important carbon-carbon double bond forming reactions, and has been used widely in the preparation of functionalized organic compounds.[1] Over the past decade, Ru-catalyzed olefin metathesis followed by a non-metathesis[2] transformation is a typical example of assisted tandem catalysis, and has been the subject of numerous publications. For example, by *in situ* conversion of a Ru-carbene into a Ru-hydride,[3] olefin metathesis can be coupled with hydrogenation[4] or isomerization.[5] The tandem transformations catalyzed by ruthenium alkylidenes developed to date include olefin metathesis, followed by cyclopropanation,[6] hydrovinylation,[7] hydroarylation,[8] aza-Michael reaction,[9] hetero-Pauson–Khand reaction,[10] and oxidation.[11]

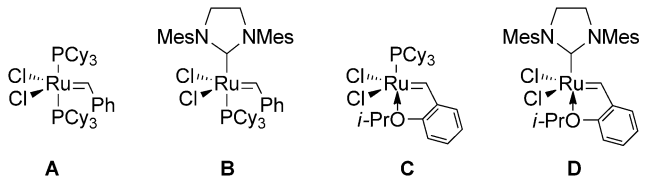
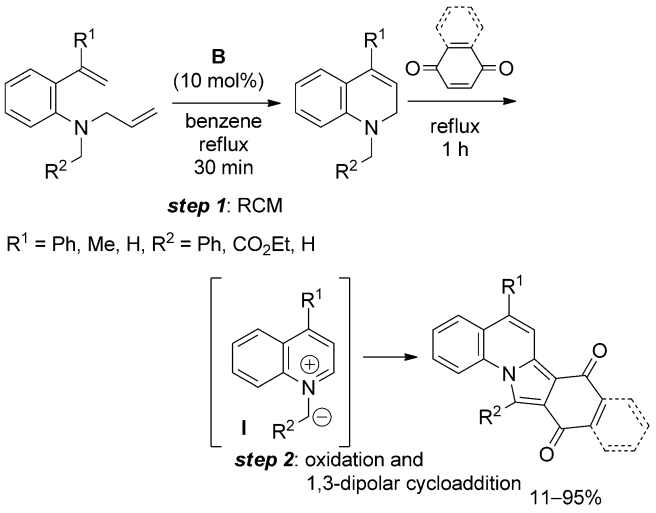


Figure 1. Ruthenium carbene catalysts.

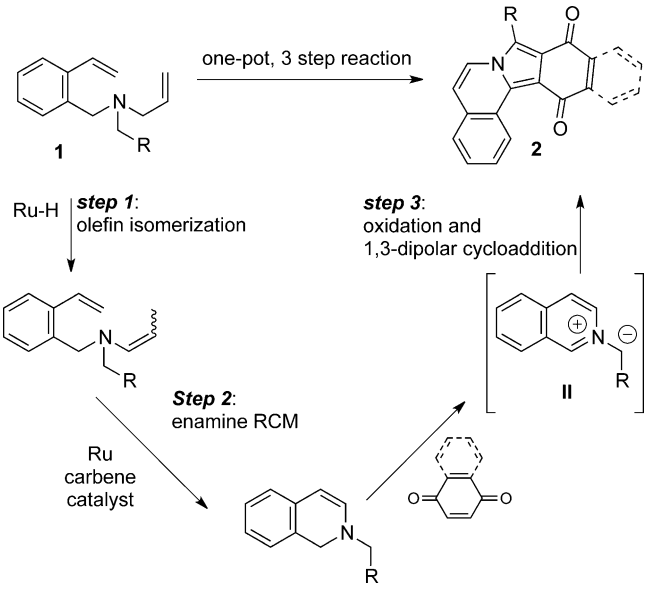
[RuClCp*] and "first generation" Grubbs metathesis complex **A** can catalyze an azide-alkyne cycloaddition reaction to give 1,5-substituted triazoles[12] and intramolecular [3+2] cycloaddition of alk-5-ynylidenecyclopropanes to give bicyclo[3.3.0]octanes.[13]

In our search for novel and efficient Ru-catalyzed reactions,[2c,3,11d,14] we developed a one-pot RCM/oxidation/1,3-dipolar cycloaddition to produce various isoindolo[2,1-*a*]quinolines (Scheme 1) from *N*-allyl-2-alkenylaniline derivatives.[15] The key intermediate in this reaction is likely to be azomethine ylide **I**, derived from the 1,2-dihydroquinoline. Azomethine ylides have also recently been used in various organic synthesis.[16] We therefore envisaged a similar 1,3-dipolar cycloaddition between a 1,3-dipolarophile and azomethine ylide **II**, generated from a 1,2-dihydroisoquinoline (Scheme 2). The enamine would be generated by a ruthenium hydride-catalyzed selective olefin isomerization of the allylamine moiety of an *N*-alkyl-*N*-(2-vinylbenzyl)prop-2-en-1-amine derivative as the first step.[17] Subsequent ruthenium alkylidene-catalyzed aliphatic enamine RCM[18] of the resulting acyclic enamine derivative, followed by oxidation and 1,3-dipolar cycloaddition would produce the corresponding isoindolo[1,2-*a*]isoquinoline **2**.

Considering the importance of streamlining syntheses towards complex molecular targets, we report



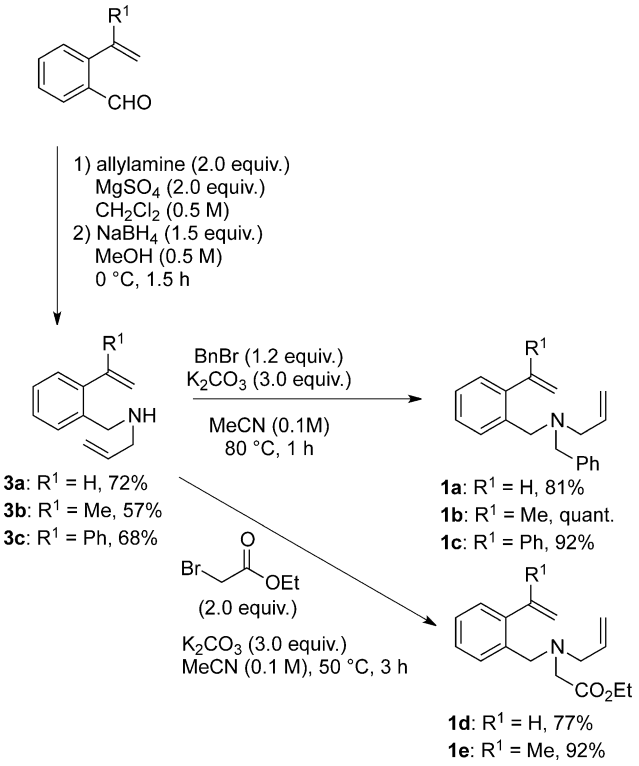
Scheme 1. Our previous work: the ring-closing metathesis (RCM)/oxidation/1,3-dipolar cycloaddition one-pot reaction.



Scheme 2. This work: the olefin isomerization/aliphatic enamine RCM/oxidation/1,3-dipolar cycloaddition one-pot reaction.

herein a one-pot olefin isomerization/aliphatic enamine RCM/oxidation/1,3-dipolar cycloaddition sequence to afford the isoindolo[1,2-*a*]isoquinoline core **2**.[19] These heterocycles are novel solution-processable π-conjugated small molecules.[20]

N-Alkyl-*N*-(2-vinylbenzyl)prop-2-en-1-amine derivatives **1** were systematically and efficiently prepared as shown in Scheme 3. Our tandem catalysis strategy was first investigated using *N*-benzyl-*N*-(2-vinylbenzyl)prop-2-en-1-amine derivative **1a**, benzoquinone, metal hydride catalysts and ruthenium carbene cata-

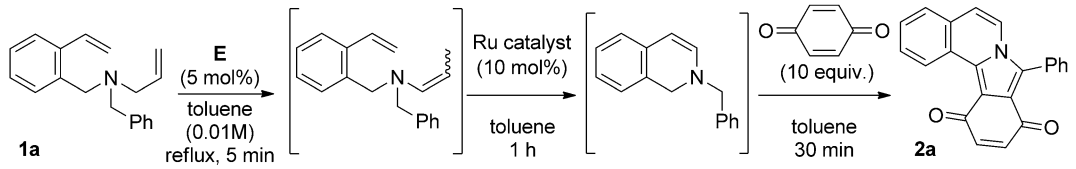


Scheme 3. Preparation of **1**.

lysts under various reaction conditions (Table 1). In the first step, isomerization of the terminal olefin, $Ru(CO)HCl(PPh_3)_3$ (**E**) was shown to be the best catalyst throughout our detailed chemical experiments. The substrate **1a** was first treated with 5 mol% of **E** in refluxing toluene for 5 min to form the corresponding acyclic aliphatic enamine derivative. The crude acyclic aliphatic enamine was treated with 10 mol% of Grubbs II catalyst (**B**) in refluxing toluene, and aliphatic enamine RCM proceeded to give the corresponding six-membered cyclic enamine. Subsequent addition of 1,4-benzoquinone (10 equiv.) gave the desired 1,3-dipolar cycloaddition product **2a** in 76% yield (entry 1). This preliminary study revealed that the proposed catalytic cascade reaction of **1a** indeed occurred to afford **2a**, probably *via* the proposed azomethine ylide intermediate. Changing the ruthenium carbene catalyst to Hoveyda–Grubbs II catalyst (**D**) increased the product yield (entries 1 and 2), but catalysts **A** and **C**, without the nitrogen-containing heterocyclic carbene (NHC) ligand, did not work in the aliphatic enamine RCM. When the enamine RCM and 1,3-dipolar cycloaddition were conducted at 80 °C or at reflux in toluene, **2a** was isolated in 72% or 77% yield, respectively (entries 3 and 4). The crystal structure of novel compound **2a** was determined by single-crystal X-ray diffraction (Figure 2).[21]

Experiments to probe the substrate scope are summarized in Table 2. A range of substituents was toler-

Table 1. Optimization of the one-pot olefin isomerization/aliphatic enamine RCM/oxidation/1,3-dipolar cycloaddition reaction.



Entry	Ru Catalyst	Aliphatic enamine RCM Temperature [°C]	[3+2] Temperature [°C]	Isolated Yield [%] for 3 steps
1	**B**	reflux	80	76
2	**D**	reflux	80	81
3	**D**	80	80	72
4	**D**	reflux	Reflux	77

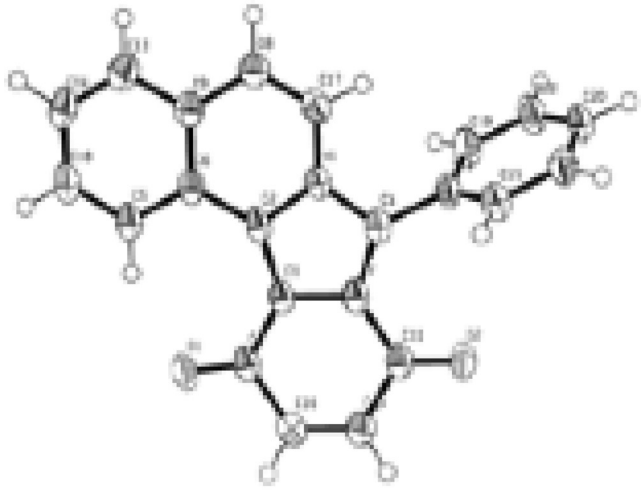
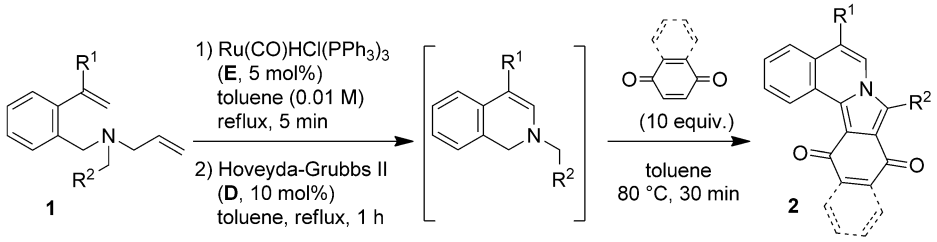


Figure 2. X-ray structure of **2a**.

ated on the nitrogen or at the α position of the styrene (entries 1–5), although the aliphatic enamine RCM of **1c**, with a phenyl group at the styrene alpha position, required 20 mol% of **D** and a longer reaction time due to the sluggish enamine metathesis.[22] Olefin isomerization of **1d** and **1e**, with ethoxycarbonylmethyl on the nitrogen, required 10 mol% of **E** and a longer reaction time. Furthermore, 1,4-naphthoquinone also worked as a 1,3-dipolarophile (entries 6–8) in this reaction.[23]

All of the obtained isoindolo[1,2-*a*]isoquinolines **2** were orange- or yellow-colored solids, while isoindolo[2,1-*a*]quinolines (Scheme 1) were red- or blue-colored solids. We then investigated the absorption and emission profiles of compounds **2a**, **b** and **d**-**h**, as shown in Figure 3 and in Figure S1 of the Supporting Information. It is interesting that the characteristic

Table 2. Scope of the one-pot olefin isomerization/aliphatic enamine RCM/oxidation/1,3-dipolar cycloaddition reaction.



Entry		R^1	R^2	Dipolarophile	Product	Yield [%] for 3 steps
1	**1a**	H	Ph	1,4-benzoquinone	**2a**	81
2	**1b**	Me	Ph	1,4-benzoquinone	**2b**	92
3[a]	**1c**	Ph	Ph	1,4-benzoquinone	**2c**	8
4[b]	**1d**	H	CO_2Et	1,4-benzoquinone	**2d**	66
5[b]	**1e**	Me	CO_2Et	1,4-benzoquinone	**2e**	57
6	**1a**	H	Ph	1,4-naphthoquinone	**2f**	49
7	**1b**	Me	Ph	1,4-naphthoquinone	**2g**	62
8[b]	**1d**	H	CO_2Et	1,4-naphthoquinone	**2h**	18

[a] 20 mol% of **D** were used and the reaction time for aliphatic enamine RCM was 24 h.
[b] In the isomerization step (1st step), 10 mol% of **E** were used and the reaction time was 2 h.

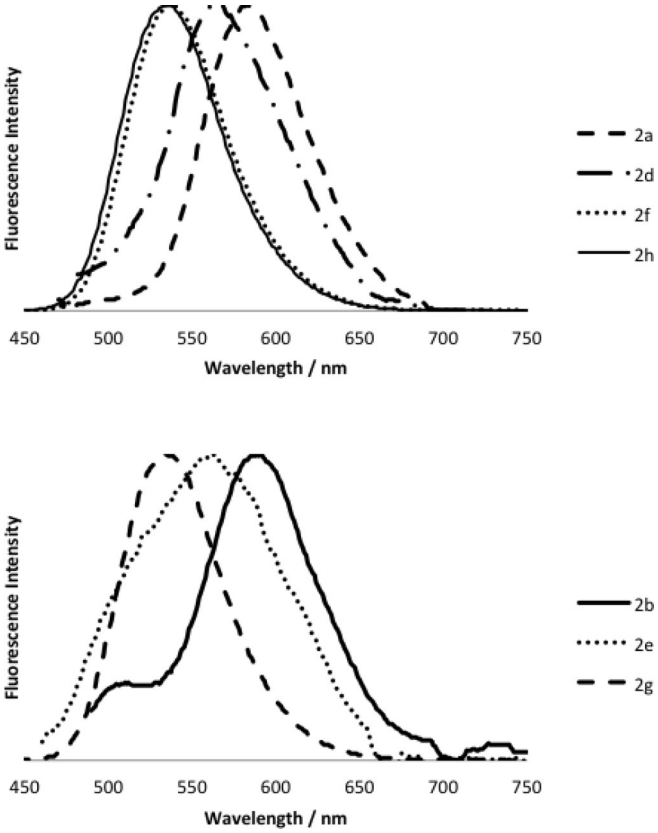


Figure 3. Fluorescence spectrum of **2** (450–750 nm) in CH_3CN. **2a**: $\varphi = 0.000511$, $\lambda_{ex} = 465$ nm, $\lambda_{em} = 583$ nm; **2b**: $\varphi = 0.000335$, $\lambda_{ex} = 470$ nm, $\lambda_{em} = 589$ nm; **2d**: $\varphi = 0.000515$, $\lambda_{ex} = 440$ nm, $\lambda_{em} = 563$ nm; **2e**: $\varphi = 0.000220$, $\lambda_{ex} = 444$ nm, $\lambda_{em} = 563$ nm; **2f**: $\varphi = 0.0752$, $\lambda_{ex} = 436$ nm, $\lambda_{em} = 537$ nm, **2g**: $\varphi = 0.137$, $\lambda_{ex} = 434$ nm, $\lambda_{em} = 535$ nm; **2h**: $\varphi = 0.337$, $\lambda_{ex} = 437$ nm, $\lambda_{em} = 535$ nm.

fluorescent absorption bands of **2** were observed from 535–583 nm with a large Stokes shift (98–123 nm) in CH_3CN. Long Stokes shift dyes can be used individually or combined with other dyes for multiplexed imaging analysis.

In summary, we have demonstrated the first example of a one-pot olefin isomerization/aliphatic enamine RCM/oxidation/1,3-dipolar cycloaddition methodology to give isoindolo[1,2-*a*]isoquinolines, which have characteristic fluorescent absorption bands with a large Stokes shift.

Experimental Section

General Information

^{1}H NMR spectra were recorded in $CDCl_3$ at 25 °C unless otherwise noted, at 300, 400 or 500 MHz, with TMS as an internal standard. ^{13}C NMR spectra were recorded in $CDCl_3$ solvent using TMS as the internal standard at 25 °C unless otherwise noted, at 100 or 125 MHz. Column chromatography was performed with silica gel 60N (spherical, neutral, 63–210 μm, Kanto Chemical Co., Inc.) unless otherwise noted. Melting points were determined on a heated plate and are uncorrected. HR-MS (*m*/*z*) were measured using MALDI (matrix assisted laser desorption/ionization) techniques unless otherwise noted.

General Procedure for *N*-Allyl-(2-vinylbenzyl)amine Derivatives (3a, 3b, and 3c)

To a solution of the *o*-vinylbenzaldehyde derivative (1.0 equiv.) and allylamine (2.0 equiv.) in CH_2Cl_2 (0.5 M) was added $MgSO_4$ (2.0 equiv.) and the mixture was stirred overnight at room temperature. The mixture was filtered through celite and the filtrate was concentrated under vacuum. The mixture was dissolved in MeOH (0.5 M) and the whole was cooled to 0 °C. To the mixture was added $NaBH_4$ (1.5 equiv.) and stirred for 1.5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl. Organic compounds were extracted with AcOEt. Organic layers were washed with brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The obtained residue was subjected to column chromatography (NH silica gel, hexane/AcOEt = 50:1) to give the corresponding **3** as an oil.

***N*-Allyl-(2-vinyl)benzylamine (3a):**[24] Amine **3a** was obtained from 2-vinylbenzaldehyde[25] (1.08 g, 8.20 mmol) as a pale yellow oil; yield: 1.02 g (5.91 mmol, 72%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51 (1H, dd, *J* = 5.9, 3.0 Hz), 7.30 (1H, dd, *J* = 5.9, 3.0 Hz), 7.26–7.22 (2H, m), 7.06 (1H, dd, *J* = 17.2, 11.0 Hz), 6.00–5.87 (1H, m), 5.68 (1H, dd, *J* = 17.5, 1.4 Hz), 5.33 (1H, dd, *J* = 11.0, 1.4 Hz), 5.20 (1H, dq, *J* = 17.2, 1.5 Hz), 5.12 (1H, dq, *J* = 10.1, 1.5 Hz), 3.83 (2H, s), 3.29 (2H, dt, *J* = 6.0, 1.5 Hz), 1.38 (1H, brs); HR-MS (MALDI): *m*/*z* = 174.12773, calcd. for $C_{12}H_{16}N$: 174.12773 $[(M+H)^+]$.

***N*-Allyl-(2-isopropenylbenzyl)amine (3b):** Amine **3b** was obtained from 2-isopropenylbenzaldehyde[25] (2.19 g, 15.0 mmol) as a colorless oil; yield: (1.61 g, 8.60 mmol, 57%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.37 (1H, m), 7.27–7.18 (2H, m), 7.15–7.10 (1H, m), 5.92 (1H, ddt, *J* = 18.8, 9.9, 5.8 Hz), 5.22–5.14 (2H, m), 5.09 (1H, dq, *J* = 9.9, 1.4 Hz), 4.88 (1H, s), 3.80 (2H, s), 3.25 (2H, d, *J* = 5.8 Hz), 2.06 (3H, dd, *J* = 1.7, 1.0 Hz), 1.44 (1H, brs); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.42, 147.27, 136.82, 128.36, 127.82, 124.91, 120.58, 115.84, 103.57, 59.75, 49.77, 40.07; HR-MS (MALDI): *m*/*z* = 188.14388, calcd. for $C_{13}H_{18}N$: 188.14351 $[(M+H)^+]$.

***N*-Allyl-[2-(α-styryl)benzyl]amine (3c):** Amine **3c** was obtained from 2-(α-styryl)benzaldehyde[26] (2.81 g, 13.5 mmol) as a pale yellow oil; yield: 2.28 g (9.16 mmol, 68%); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 (1H, d, *J* = 7.4 Hz), 7.34 (1H, dd, *J* = 7.7, 6.6 Hz), 7.32–7.25 (7H, m), 5.77 (1H, d, *J* = 1.1 Hz) 5.76–5.70 (1H, m), 5.25 (1H, d, *J* = 1.1 Hz), 5.03 (1H, dd, *J* = 17.0, 1.4 Hz), 4.99 (1H, dd, *J* = 10.4, 1.4 Hz), 3.52 (2H, s), 3.02 (2H, d, *J* = 6.3 Hz), 1.20 (1H, brs); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.63, 140.85, 140.47, 137.70, 136.44, 129.98, 128.95, 128.07, 127.48, 126.56, 126.14, 115.29, 114.87, 51.48, 50.60; HR-MS (MALDI): *m*/*z* = 250.15903, calcd. for $C_{18}H_{20}N$: 250.15902 $[(M+H)^+]$.

General Procedure for *N*-Allyl-*N*-benzyl-(2-vinylbenzyl)amine Derivatives (1a, 1b, and 1c)

To a solution of **3a–c** (1.0 equiv.) in CH_3CN (0.1 M) were added K_2CO_3 (3.0 equiv.) and benzyl bromide (1.2 equiv.) and stirred at 80 °C for 1 h. The mixture was cooled to room temperature. The whole was quenched by saturated K_2CO_3 in ethylene glycol then stirred overnight. Organic compounds were extracted with AcOEt. Organic layers were washed with brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The obtained residue was subjected to column chromatography (acid silica gel, hexane/AcOEt = 50:1) to give **1a–c** as oils.

***N*-Allyl-*N*-benzyl-(2-vinylbenzyl)amine (1a):** Amine **1a** was obtained from **3a** (86.7 mg, 0.500 mmol) as a colorless oil; yield: 107 mg (0.406 mmol, 81%); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44–7.41 (1H, m), 7.31–7.29 (1H, m), 7.26–7.19 (4H, m), 7.16–7.12 (3H, m), 7.04 (1H, dd, J = 17.4, 10.9 Hz), 5.87–5.81 (1H, m), 5.53 (1H, dd, J = 17.4, 1.9 Hz), 5.16 (1H, dd, J = 10.9, 1.9 Hz), 5.13–5.06 (2H, m), 3.53 (2H, s), 3.47 (2H, s), 2.95 (2H, d, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.60, 137.63, 136.46, 135.65, 134.99, 130.19, 128.92, 128.74, 128.16, 128.09, 127.35, 127.17, 126.79, 125.59, 117.61, 114.72, 57.85, 56.44, 55.92; HR-MS (MALDI): m/z = 264.17468, calcd. for $C_{19}H_{22}N$: 264.17471 [$(M+H)^+$]; anal. calcd. for $C_{19}H_{21}N$: C 86.64, H 8.04, N 5.32; found: C 86.88, H 8.01, N, 5.12.

***N*-Allyl-*N*-benzyl-(2-isopropenylbenzyl)amine (1b):** Amine **1b** was obtained from **3b** (281 mg, 1.50 mmol) as a colorless oil; yield: 422 mg (1.52 mmol, quant); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (1H, d, J = 7.4 Hz), 7.35 (2H, d, J = 7.4 Hz), 7.29 (1H, d, J = 7.7 Hz), 7.26–7.21 (2H, m), 7.20–7.16 (1H, m), 7.08 (1H, dd, J = 7.4, 1.1 Hz), 5.88 (1H, ddt, J = 17.2, 10.3, 5.7 Hz), 5.18 (1H, dd, J = 17.2, 1.7 Hz), 5.14 (1H, d, J = 1.7 Hz), 5.11 (1H, dd, J = 10.3, 1.7 Hz), 4.77 (1H, d, J = 1.7 Hz), 3.59 (2H, s), 3.54 (2H, s), 3.01 (2H, d, J = 5.7 Hz), 2.02 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.22, 144.00, 139.78, 136.30, 136.12, 128.96, 128.73, 128.10, 127.80, 126.80, 126.70, 126.31, 117.13, 114.87, 58.00, 56.46, 54.83, 25.21; HR-MS (MALDI): m/z = 278.19033, calcd. for $C_{20}H_{24}N$: 278.19045 [$(M+H)^+$]; anal. calcd. for $C_{20}H_{23}N$: C 86.59, H 8.36, N 5.05; found: C 86.69, H 8.48, N 5.02.

***N*-Allyl-*N*-benzyl-[2-(α-styryl)benzyl]amine (1c):** Amine **1c** was obtained from **3c** (125 mg, 0.500 mmol) as a pale yellow oil; yield: 154 mg (0.452 mmol, 90%); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (1H, d, J = 7.4 Hz), 7.27 (1H, d, J = 7.4 Hz), 7.21–7.15 (10H, m), 7.11 (2H, m), 5.71–5.65 (1H, m), 5.68 (1H, d, J = 1.1 Hz), 5.07 (1H, d, J = 1.1 Hz), 5.00 (1H, dd, J = 17.5, 1.4 Hz), 4.96 (1H, dd, J = 10.3, 1.4 Hz), 3.30 (2H, s), 3.28 (2H, s), 2.79 (2H, d, J = 5.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.61, 141.40, 140.68, 139.70, 137.91, 135.96, 130.06, 128.79, 128.65, 128.25, 128.04, 127.55, 126.61, 126.52, 126.41, 117.02, 115.00, 57.72, 56.18, 55.02; HR-MS (MALDI): m/z = 340.20598, calcd. for $C_{25}H_{26}N$: 340.20620 [$(M+H)^+$]; anal. calcd. for $C_{25}H_{25}N$: C 88.45, H 7.42, N 4.13; found: C 88.39, H 7.57, N 4.16.

General Procedure for Ethyl-*N*-allyl-*N*-ethoxycarbonylmethyl(2-vinylbenzyl)amine Derivatives (1d and 1e)

To a solution of **3a**, **3b** (0.5 equiv.) in CH_3CN (0.1 M) were added K_2CO_3 (3.0 equiv.) and ethyl bromoacetate (2.0 equiv.) and stirred at 50 °C for 3 h. To the mixture was added saturated K_2CO_3 in EtOH. The mixture was filtrated through celite, then organic compounds were extracted with AcOEt. Organic layers were washed with brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The obtained residue was subjected to column chromatography (acid silica gel, hexane/AcOEt = 99:1) to give **1d, 1e** each as an oil.

***N*-Allyl-*N*-ethoxycarbonylmethyl-(2-vinylbenzyl)amine (1d):** Amine **1d** was obtained from **3a** (86.6 mg, 0.500 mmol) as a colorless oil; yield: 77.6 mg, 0.298 mmol, 59%); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.52 (1H, d, J = 7.4 Hz), 7.32 (1H, d, J = 6.9 Hz), 7.27–7.19 (3H, m), 5.87 (1H, m), 5.64 (1H, d, J = 17.8 Hz), 5.28 (1H, d, J = 10.9 Hz), 5.22 (1H, d, J = 17.2 Hz), 5.22 (1H, d, J = 9.7 Hz), 4.14 (2H, q, J = 7.1 Hz), 3.84 (2H, s), 3.30 (2H, d, J = 6.3 Hz), 3.29 (2H, s), 1.26 (3H, t, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.46, 137.85, 135.61, 134.69, 130.39, 127.48, 127.45, 125.59, 117.91, 115.14, 60.15, 56.87, 55.44, 53.38, 14.26; HR-MS (MALDI): m/z = 260.16451, calcd. for $C_{16}H_{22}NO_2$: 260.16484 [$(M+H)^+$].

***N*-Allyl-*N*-ethoxycarbonylmethyl-(2-isopropenylbenzyl)-amine (1e):** Amine **1e** was obtained from **3b** (93.6 mg, 0.500 mmol) as a colorless oil; yield: 125 mg (0.457 mmol, 92%); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.55 (1H, d, J = 7.4 Hz), 7.25–7.18 (2H, m), 7.10 (1H, dd, J = 7.4, 1.7 Hz), 5.87–5.81 (1H, m), 5.20 (1H, dd, J = 17.2, 1.7 Hz), 5.16 (1H, d, J = 1.1 Hz), 5.13 (1H, dd, J = 10.8, 1.7 Hz), 4.78 (1H, d, J = 1.1 Hz), 4.13 (2H, q, J = 7.2 Hz), 3.80 (2H, s), 3.29 (2H, s), 3.26 (2H, d, J = 5.7 Hz), 2.03 (3H, s), 1.25 (3H, t, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.59, 145.28, 144.22, 135.86, 135.61, 129.32, 127.91, 126.81, 126.63, 117.64, 114.73, 60.14, 56.84, 54.80, 53.68, 25.19, 14.25; HR-MS (MALDI): m/z = 274.18016, calcd. for $C_{17}H_{24}NO_2$: 274.18024 [$(M+H)^+$].

General Procedure for 8-Phenylisoindolo[1,2-*a*]isoquinoline-9,12-diones (2a–c, 2f and 2g)

To a solution of **1** (1.0 equiv.) in toluene (0.01 M) was added $Ru(CO)HCl(PPh_3)_3$ (5 mol%) in a glove box. The mixture was refluxed for 5 min. To the mixture was added Hoveyda–Grubbs II (10 mol%) and the mixture was continuously stirred for 1 h. The mixture was cooled to 80 °C. To the mixture was added quinone (10 equiv.) and the whole was continuously stirred for 30 min. The mixture was carried out from the glove box and was quenched by saturated aqueous NH_4Cl. Organic compounds were extracted with AcOEt. Organic layers were washed with brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The obtained residue was subjected to column chromatography (neutral flash silica gel, hexane/AcOEt = 24:1→hexane/toluene/AcOEt = 9:10:1) to give the corresponding product **2** as a powder.

8-Phenylisoindolo[1,2-*a*]isoquinoline-9,12-dione (2a): Product **2a** was obtained from **1a** (26.3 mg, 0.100 mmol) as

a red powder; yield: 26.2 mg (0.0808 mmol, 81%; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 10.26$ (1H, d, $J = 8.6$ Hz), 7.73–7.71 (2H, m), 7.68–7.67 (2H, m), 7.61–7.57 (3H, m), 7.54–7.53 (2H, m), 7.04 (1H, d, $J = 7.4$ Hz), 6.90 (1H, d, $J = 10.0$ Hz), 6.66 (1H, d, $J = 10.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 183.10, 180.65, 142.56, 137.93, 133.43, 131.66, 130.73, 129.91, 129.89, 128.98, 128.55, 128.38, 128.08, 126.86, 125.68, 121.56, 120.36, 116.24, 113.26; HR-MS (MALDI): $m/z = 324.10191$, calcd. for $C_{22}H_{14}NO_2$: 324.10201 [$(M+H)^+$]; anal. calcd. for $C_{22}H_{14}NO_2 + 0.1\,H_2O$: C 81.27, H 4.09, N 4.31; found: C 80.97, H 4.22; N, 4.23; mp 235.0–236.0 (recrystallized from hexane/AcOEt, a red column crystal).

5-Methyl-8-phenylisoindolo[1,2-*a*]isoquinoline-9,12-dione (2b): Product **2b** was obtained from **1b** (27.7 mg, 0.100 mmol) as a red powder; yield: 31.2 mg (0.0922 mmol, 92%); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 10.34$ (1H, dd, $J =$ 7.7, 1.1 Hz), 7.80 (1H, dd, $J = 7.7$, 1.4 Hz), 7.76–7.71 (2H, m), 7.62–7.57 (4H, m), 7.55–7.53 (2H, m), 6.89 (1H, d, $J =$ 10.0 Hz), 6.65 (1H, d, $J = 10.0$ Hz), 2.42 (3H, d, $J = 1.1$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 183.17$, 180.59, 142.59, 137.82, 133.22, 131.26, 130.76, 130.62, 129.92, 129.81, 128.98, 128.57, 128.36, 128.31, 123.40, 122.43, 120.21, 119.64, 113.04, 16.75; HR-MS (MALDI): $m/z = 338.11756$, calcd. for $C_{23}H_{16}NO_2$: 338.11771 [$(M+H)^+$]; mp 243.5–244.5 (recrystallized from hexane/AcOEt, a red needle crystal).

5,8-Diphenylisoindolo[1,2-*a*]isoquinoline-9,12-dione (2c): To a solution of **1c** (33.9 mg, 0.100 mmol) in toluene (0.01 M) was added $Ru(CO)HCl(PPh_3)_3$ (4.8 mg, 5.00 mmol, 5 mol%) in a glove box. The mixture was refluxed for 5 min. To the mixture was added Hoveyda–Grubbs II (12.6 mg, 0.0200 mmol, 20 mol%) and the mixture was continuously stirred for 24 h. The mixture was cooled to 80 °C. To the mixture was added 1,4-benzoquinone (10 equiv.) and the whole was continuously stirred for 30 min. The mixture was carried out from glove box and was quenched by saturated aqueous NH_4Cl. Organic compounds were extracted with AcOEt. Organic layers were washed with brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The obtained residue was subjected to column chromatography (neutral flash silica gel, hexane/AcOEt = 24:1→ hexane/toluene/AcOEt = 9:10:1) to give **2c** as a red powder; yield: 3.1 mg 0.00776 mmol (8%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 10.51$ (1H, d, $J = 8.2$ Hz), 8.46 (1H, dd, $J = 7.7$, 1.4 Hz), 8.17 (1H, dd, $J = 7.7$, 1.1 Hz), 7.81–7.74 (3H, m), 7.72–7.58 (8H, m), 7.09 (1H, d, $J = 7.3$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 183.11$, 180.69, 142.66, 137.94, 135.90, 133.11, 131.77, 130.68, 129.98, 129.89, 129.27, 129.06, 128.71, 128.53, 128.38, 128.29, 128.20, 125.82. 125.63, 122.84, 121.91, 120.58, 120.41, 113.08; HR-MS (MALDI): $m/z = 400.13321$, calcd. for $C_{28}H_{18}NO_2$: 400.13345 [$(M+H)^+$].

8-Phenylbenzo[5,6]isoindolo[1,2-*a*]isoquinoline-9,14-dione (2f): Product **2f** was obtained from **1a** (26.3 mg, 0.100 mmol) as an orange powder; yield: 18.2 mg (0.0486 mmol, 49%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 10.51$ (1H, d, $J = 8.6$ Hz), 8.46 (1H, d, $J = 8.6$ Hz), 8.17 (1H, d, $J =$ 7.4 Hz, 7.80–7.78 (1H, m), 7.76 (1H, d, $J = 7.4$ Hz), 7.69–7.61 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 181.44$, 178.92, 136.92, 134.66, 133.90, 133.69, 133.47, 132.54, 131.80, 130.86, 129.85, 129.82, 129.65, 129.05, 128.47, 128.44, 127.49, 127.03, 126.88, 126.21, 125.98, 121.64, 116.54, 114.59; HR-MS (MALDI): $m/z = 374.11756$, calcd. for $C_{26}H_{16}NO_2$: 374.11728 [$(M+H)^+$]; anal. calcd. for $C_{26}H_{15}NO_2 + 0.3\,H_2O$: C 82.44, H 4.15, N 3.70; found: C 82.48, H 4.24, N 3.87; mp 272.0–273.0 °C (recrystallized from hexane/toluene, a yellow needle crystal).

5-Methyl-8-phenylbenzo[5,6]isoindolo[1,2-*a*]isoquinoline-9,14-dione (2g): Product **2g** was obtained **1b** (27.7 mg, 0.100 mmol) as an orange powder; yield: 24.2 mg (0.0623 mmol, 62%); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 10.59$ (1H, d, $J = 7.4$ Hz), 8.45–8.44 (1H, m), 8.15 (1H, dd, $J = 7.4$, 1.1 Hz), 7.83–7.71 (4H, m), 7.67–7.57 (7H, m), 2.44 (3H, d, $J = 1.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): $\delta = 181.40$, 178.91, 137.25, 134.96, 133.52, 133.31, 132.38, 131.34, 131.01, 130.68, 129.70, 129.61, 129.50, 129.02, 128.84, 128.30, 127.55, 126.23, 126.12, 123.35, 122.68, 121.75, 119.85, 114.63, 16.65; HR-MS (MALDI): $m/z = 388.13321$, calcd. for $C_{27}H_{18}NO_2$: 388.13386 [$(M+H)^+$]; anal. calcd. for $C_{27}H_{17}NO_2$: C 83.70, H 4.42, N 3.62; found: C 83.55, H 4.60, N 3.64; mp 266.5–267.0 (recrystallized from hexane/toluene, an orange needle crystal).

General Procedure for 8-Ethoxycarbonylisoindolo[1,2-*a*]isoquinoline-9,12-diones (2d, 2e, and 2h)

To a solution of **1d** or **1e** (1.0 equiv.) in toluene (0.1 M) was added $Ru(CO)HCl(PPh_3)_3$ (10 mol%) in a glove box. The mixture was refluxed for 2 h. The mixture was diluted by the addition of toluene (0.1 M→0.01 M), then to the mixture was added Hoveyda–Grubbs II (10 mol%) and the mixture was continuously stirred for 1 h. The mixture was cooled to 80 °C. To the mixture was added quinone (10 equiv.) and the whole was continuously stirred for 30 min. The mixture was carried out from the glove box and was quenched by saturated aqueous NH_4Cl. Organic compounds were extracted with AcOEt. Organic layers were washed with brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The obtained residue was subjected to column chromatography (neutral flash silica gel, hexane/AcOEt = 24:1→hexane/toluene/AcOEt = 9:10:1) to give **2d**, **2e** or **2h** as a powder.

8-Ethoxycarbonylisoindolo[1,2-*a*]isoquinoline-9,12-dione (2d): Product **2d** was obtained from **1d** (25.9 mg, 0.100 mmol) as an orange powder; yield: 21.2 mg (0.0662 mmol, 66%); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 10.21$ (1H, d, $J = 7.4$ Hz), 8.59 (1H, d, $J = 7.4$ Hz), 7.77–7.70 (3H, m), 7.26 (1H, d, $J = 7.4$ Hz), 6.89 (1H, d, $J = 10.3$ Hz), 6.77 (1H, d, $J = 10.3$ Hz), 4.57 (2H, q, $J = 7.3$ Hz), 1.51 (3H, t, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 182.01$, 180.46, 161.19, 141.64, 137.49, 134.32, 130.39, 129.79, 128.61, 126.90, 125.02, 124.69, 122.81, 119.11, 117.33, 113.74, 62.42, 13.90; HR-MS (FAB): $m/z = 320.0905$, calcd. for $C_{19}H_{14}NO_4$ [$(M+H)^+$]: 320.0922; anal. calcd. for $C_{19}H_{13}NO_4 + 0.1\,H_2O$: C 71.07, H 4.14, N 4.36; found: C 71.13, H 4.23, N 4.31; mp 175.5–176.5 (from hexane/AcOEt, a red column crystal).

5-Methyl-8-ethoxycarbonylisoindolo[1,2-*a*]isoquinoline-9,12-dione (2e): Product **2e** was obtained from **1e** (27.4 mg, 0.100 mmol) as an orange powder; yield: 19.1 mg (0.0568 mmol, 57%); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 10.19–10.18 (1H, m), 8.38 (1H, s), 7.81–7.80 (1H, m), 7.74–7.70 (2H, m), 6.83 (1H, d, $J = 10.3$ Hz), 6.71 (1H, d, $J =$ 10.3 Hz), 4.56 (2H, q, $J = 7.2$ Hz), 2.52 (3H, s), 1.51 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 182.07$, 180.34, 161.32, 141.63, 137.29, 133.94, 130.42, 130.32, 128.48, 128.34, 124.80, 124.39, 123.67, 123.37, 120.92, 118.67, 113.47, 62.34,

16.80, 13.90; HR-MS (MALDI): $m/z = 334.10738$, calcd. for $C_{20}H_{16}NO_4$ $[(M+H)^+]$: 334.10731; anal. calcd. for $C_{20}H_{15}NO_4 + 0.2\,H_2O$: C 71.29, H 4.61, N 4.16; found: C 71.68, H 4.57, N 4.12; mp 158.0–159.0 (from hexane/AcOEt, a red needle crystal).

8-Ethoxycarbonylmethylbenzo[5,6]isoindolo[1,2-*a*]isoquinoline-9,14-dione (2h): Product **2h** was obtained from **1d** (25.9 mg, 0.100 mmol) as a yellow powder; yield: 6.6 mg (0.0179 mmol, 18%); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 10.42$ (1H, d, $J = 7.8$ Hz), 8.51 (1H, d, $J = 7.4$ Hz), 8.41 (1H, d, $J = 7.4$ Hz), 8.24 (1H, t, $J = 4.4$ Hz), 7.87–7.69 (2H, m), 7.29 (4H, t, $J = 6.2$ Hz), 4.62 (2H, q, $J = 7.2$ H), 1.54 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 180.58$, 178.91, 161.64, 136.23, 134.88, 134.65, 134.27, 133.93, 133.76, 132.87, 130.20, 128.63, 127.55, 127.38, 127.06, 126.98, 126.50, 126.47, 126.07, 125.47, 122.76, 117.63, 115.16, 62.57, 14.00; HR-MS (MALDI): $m/z = 392.08933$, calcd. for $C_{23}H_{15}NO_4Na$ $[(M+Na)^+]$: 392.08924; m.p. 268.0–269.0 °C (recrystallized from hexane/toluene, an orange needle crystal).

Experiments for Measurement of Photochemical Properties[27]

A 5 mM DMSO stock solution of each compound was prepared. Each spectrum was maesured by using diluted stock solution of the desired solvent. For determination of the quantum efficiency of fluorescence (ΦF), fluorescein in 0.1 M aqueous NaOH was used as a fluorescence standard. The quantum efficiency of fluorescence was obtained with the following equation (F denotes fluorescence intensity at each wavelength, Σ[F] was calculated by summation of fluorescence intensity and n denotes refractive index of the solvents): $\Phi F_{sample} = \Phi F_{standard} \times Abs_{standard} \Sigma[F_{sample}]/Abs_{sample} \times \Sigma[F_{standard}] \times (n_{sample}/n_{standard})^2$.

Supporting Information

Spectral data for all new compounds, absorption spectra of compounds **2**, as well as the X-ray structures of compounds **2d** and **2e** are available in the Supporting Information.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (MEXT), ACT-C from Japan Science and Technology Agency (JST) and Takeda Science Foundation.

References

[1] a) G. C. Vougioukalakis, R. H. Grubbs, *Chem. Rev.* **2010**, *110*, 1746–1787; b) S. P. Nolan, H. Clavier, *Chem. Soc. Rev.* **2010**, *39*, 3305–3316.

[2] For reviews, see: a) B. Alcaide, P. Almendros, *Chem. Eur. J.* **2003**, *9*, 1258–1262; b) B. Schmidt, *Eur. J. Org. Chem.* **2004**, 1865–1880; c) M. Arisawa, Y. Terada, K. Takahashi, M. Nakagawa, A. Nishida, *Chem. Rec.* **2007**, *7*, 238–253; d) B. Alcaide, P. Almendros, A. Luna, *Chem. Rev.* **2009**, *109*, 3817–3858; e) B. Schmidt, S. Krehl, *Domino- and tandem olefin metathesis reactions*, in: *Olefin Metathesis – Theory and Practice*, (Ed.: K. Grela), Wiley, Weinheim, **2014**, pp 187–232.

[3] M. Arisawa, Y. Terada, K. Takahashi, M. Nakagawa, A. Nishida, *J. Org. Chem.* **2006**, *71*, 4255–4261.

[4] J. Louie, C. W. Bielawski, R. H. Grubbs, *J. Am. Chem. Soc.* **2001**, *123*, 11312–11313.

[5] A. E. Sutton, B. A. Seigal, D. F. Finnegan, M. L. Snapper, *J. Am. Chem. Soc.* **2002**, *124*, 13390–13391.

[6] B. G. Kim, M. L. Snapper, *J. Am. Chem. Soc.* **2006**, *128*, 52–53.

[7] J. Gavenonis, R. V. Arroyo, M. L. Snapper, *Chem. Commun.* **2010**, *46*, 5692–5694.

[8] J.-R. Chen, C.-F. Li, X.-L. An, J.- J. Zhang, X.-Y. Zhu, W.-J. Xiao, *Angew. Chem.* **2008**, *120*, 2523–2526; *Angew. Chem. Int. Ed.* **2008**, *47*, 2489–2492.

[9] S. Fustero, D. Jiménez, M. Sánchez-Roselló, C. del Pozo, *J. Am. Chem. Soc.* **2007**, *129*, 6700–6701.

[10] D. F. Finnegan, M. L. Snapper, *J. Org. Chem.* **2011**, *76*, 3644–3653.

[11] a) S. Beligny, S. Eibauer, S. Maechling, S. Blechert, *Angew. Chem.* **2006**, *118*, 1933–1937; *Angew. Chem. Int. Ed.* **2006**, *45*, 1900–1903; b) A. A. Scholte, M. H. An, M. L. Snapper, *Org. Lett.* **2006**, *8*, 4759–4762; c) B. Schmidt, S. Krehl, *Chem. Commun.* **2011**, *47*, 5879–5881; d) H. Kato, T. Ishigame, N. Oshima, M. Arisawa, S. Shuto, *Adv. Synth. Catal.* **2011**, *353*, 2676–2680.

[12] a) L. Zhang, X. G. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin, G. C. Jia, *J. Am. Chem. Soc.* **2005**, *127*, 15998–15999; b) B. C. Boren, S. Narayan, L. K. Rasmussen, L. Zhang, H. T. Zhao, Z. Y. Lin, G. C. Jia, V. V. Fokin, *J. Am. Chem. Soc.* **2008**, *130*, 8923–8930; for a study focused on the regioselectivity of internal alkynes in this reaction see also: c) M. M. Majireck, S. M. Weinreb, *J. Org. Chem.* **2006**, *71*, 8680–8683; d) S. Grecian, V. V. Fokin, *Angew. Chem.* **2008**, *120*, 8409–8411; *Angew. Chem. Int. Ed.* **2008**, *47*, 8285–8287.

[13] F. López, A. Delgado, J. R. Rodríguez, L. Castedo, J. L. Mascareñas, *J. Am. Chem. Soc.* **2004**, *126*, 10262–10263.

[14] a) M. Arisawa, Y. Terada, M. Nakagawa, A. Nishida, *Angew. Chem.* **2002**, *114*, 4926–4928; *Angew. Chem. Int. Ed.* **2002**, *41*, 4732–4734; b) Y. Terada, M. Arisawa, M. Nakagawa, A. Nishida, *Angew. Chem.* **2004**, *116*, 4155–4159; *Angew. Chem. Int. Ed.* **2004**, *43*, 4063–4067; c) K. Kajihara, M. Arisawa, S. Shuto, *J. Org. Chem.* **2008**, *73*, 9494–9496; d) T. Ogawa, T. Nakamura, T. Araki, K. Yamamoto, S. Shuto, M. Arisawa, *Eur. J. Org. Chem.* **2012**, 3084–3087.

[15] M. Arisawa, Y. Fujii, H. Kato, H. Fukuda, T. Matsumoto, M. Ito, H. Abe, Y. Ito, S. Shuto, *Angew. Chem.* **2013**, *125*, 1037–1041; *Angew. Chem. Int. Ed.* **2013**, *52*, 1003–1006; the obtained isoindolo[2,1-*a*]quinoline skeleton from the one-pot RCM/oxidation/1,3-dipolar cycloaddition is a novel fluorescent chromophore.

[16] D. Seidle, *Acc. Chem. Res.* **2015**, *48*, 317–328.

[17] S. Krompiec, M. Krompiec, R. Penczek, H. Ignasiak, *Coord. Chem. Rev.* **2008**, *252*, 1819–1841.

[18] During this research project, Liu in Boston College reported the first example of aromatic enamine RCM; S. Xu, F. Haeffner, B. Li, L. N. Zakharov, S. Liu, *Angew.*

Chem. **2014**, *126*, 6913–6917; *Angew. Chem. Int. Ed.* **2014**, *53*, 6795–6799.
[19] Chemistry, including preparation and reactivity, of aromatic enamines and aliphatic enamines are different.
[20] a) C. R. Lee, Y. Lin, L. Lin, C. Li, T. Chu, S. Sun, J. T. Lin, K. Ho, *RSC Adv.* **2015**, *5*, 23810–23825; b) Z. Guo, S. Park, J. Yoon, I. Shin, *Chem. Soc. Rev.* **2014**, *43*, 16–29.
[21] CCDC 1062688 contains the supplementary crystallographic data for **2a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. X-ray structures of **2d** (CCDC 1062689) and **2e** (CCDC 1062690) are shown in the Supporting Information.
[22] The olefin isomerization of compound **1c** proceeded quantitatively. However, the subsequent aliphatic enamine RCM did not proceed very well.
[23] Although we screened some combinations of oxidant and 1,3-dipolalophile, at this stage, quinones work well in this one-pot reaction. This is why we need an excess amount of benzoquinones.
[24] B. Bradshaw, P. Evans, J. Fletcher, A. T. Lee, P. G. Mwashimba, D. Oehlrich, E. Thomas, R. H. Davies, B. C. P. Allen, K. J. Broadley, A. Hamrounic, C. Escargueilc, *Org. Biomol. Chem.* **2008**, *6*, 2138–2157.
[25] E. Peyronx, F. Berthol, H. Doucet, M. Santelli, *Eur. J. Org. Chem.* **2004**, 1075–1082.
[26] K. Kundu, J. V. McCullagh, A. T. Morehead Jr, *J. Am. Chem. Soc.* **2005**, *127*, 16042–16043.
[27] T. Kobayashi, Y. Urano, M. Kamiya, T. Ueno, H. Kojima, T. Nagano, *J. Am. Chem. Soc.* **2007**, *129*, 6696–6697.

