Ruthenium Catalysis

DOI: 10.1002/anie.201206765

One-Pot Ring-Closing Metathesis/1,3-Dipolar Cycloaddition through Assisted Tandem Ruthenium Catalysis: Synthesis of a Dye with Isoindolo[2,1-*a*]quinoline Structure**

Mitsuhiro Arisawa, Yuki Fujii, Hiroshige Kato, Hayato Fukuda, Takashi Matsumoto, Mika Ito, Hiroshi Abe, Yoshihiro Ito, and Satoshi Shuto**

Assisted tandem catalytic reactions are defined as catalyzed reaction sequences that proceed through more than one mechanism, but with just one precatalyst.[1] In these reactions, the catalyst of the first cycle is transformed into the catalyst of the second cycle by a chemical initiator, for example, an additive that induces an organometallic transformation in situ. Over the past decade, several reaction sequences comprising an olefin-metathesis step and a subsequent non-metathesis[2] transformation of the newly generated carbon=carbon bond were developed. For example, olefin metathesis can be combined with hydrogenation[3] or isomerization[4] by in situ conversion of a Ru–carbene into a Ru–hydride.[5] Ruthenium–alkylidene-catalyzed tandem transformations that were developed to date include olefin metathesis, followed by cyclopropanation,[6] hydrovinylation,[7] hydroarylation,[8] the aza-Michael reaction,[9] the hetero-Pauson–Khand reaction,[10] or oxidation.[11]

On the other hand, [RuClCp*] and the "first generation" Grubbs metathesis complex **A** (Figure 1) catalyze an azide–alkyne cycloaddition reaction to give 1,5-substituted triazoles,[12] and an intramolecular [3+2] cycloaddition of alk-5-ynylidenecyclopropanes to give bicyclo[3.3.0]octane,[13] respectively.

In our search for novel and efficient Ru-catalyzed reactions,[2c,3,11d,14] we developed a one-pot ring-closing metathesis/oxidation methodology to produce various 2-quinolones from *N*-allyl-2-vinylaniline derivatives (Scheme 1).[11d] Oxidation of the α-methylene group of amines to the corresponding amides is very difficult.[15] The key intermediate in this reaction might be the azomethine ylide **I**, equivalent to 1,2-dihydroquinoline. If the azomethine ylide is generated as the intermediate, we envisaged 1,3-dipolar cycloaddition of azomethine ylide from the 1,2-dihydroquinoline, generated by a ruthenium–alkylidene-catalyzed ring-closing metathesis (RCM) of an *N*-alkyl-*N*-allyl-2-vinylaniline derivative as the first step in the tandem reaction, with 1,3-dipolarophile would be proceeded by the active ruthenium species derived from the catalyst precursor, the ruthenium–alkylidene catalyst.

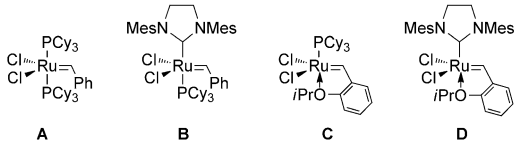
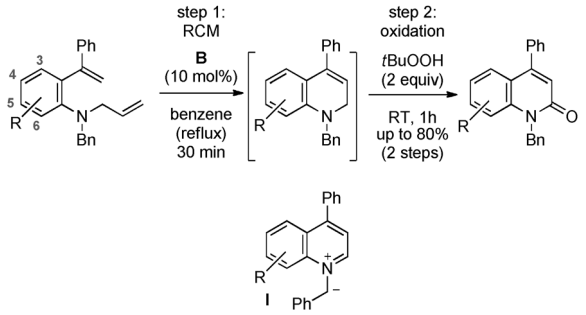


Figure 1. Ruthenium alkylidenes. Cy = cyclohexyl, Mes = 2,4,6-trimethylphenyl.



Scheme 1. One-pot RCM/oxidation reaction. Bn = benzyl.

Considering the importance of streamlining syntheses toward complex molecular targets, we report herein a new tandem process that combines a ruthenium-catalyzed RCM with a ruthenium-catalyzed intermolecular 1,3-dipolar cycloaddition to afford an isoindolo[2,1-a]quinoline core. These heterocycles are novel solution-processable π-conjugated small molecules whose color can be altered dramatically by exchanging a substituent on the core.

Our tandem-catalysis strategy was first examined using *N*-allyl-*N*-benzyl-2-vinylaniline derivative **1a**, dipolarophile **3a**, and second-generation Grubbs catalyst **B** under various reaction conditions (Table 1). Compound **1a** was first treated with **B** (10 mol%) in benzene (reflux) for 30 min to form the corresponding 1,2-dihydroquinoline derivative **2a**.[16] When

[*] Dr. M. Arisawa, Y. Fujii, H. Kato, Dr. H. Fukuda, Dr. T. Matsumoto, M. Ito, Dr. H. Abe, Dr. Y. Ito, Prof. Dr. S. Shuto
Faculty of Pharmaceutical Sciences, Hokkaido University
Kita 12, Nishi 6, Kita-ku, Sapporo 060-0812 (Japan)
and
Rigaku Corporation, X-ray Research Laboratory
3-9-12 Matsubara-cho, Akishima, Tokyo 196-8666 (Japan)
and
Nano Medical Engineering Laboratory
RIKEN Advanced Science Institute
2-1, Hirosawa, Wako-shi, Saitama 351-0198 (Japan)

[**] This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Molecular Activation Directed toward Straightforward Synthesis" from the Ministry of Education, Culture, Sports, Science, and Technology (Japan) (MEXT) and ACT-C from Japan Science and Technology Agency (JST).

Supporting information for this article (including experimental procedures and full characterization of compounds) is available on the WWW under http://dx.doi.org/10.1002/anie.201206765.

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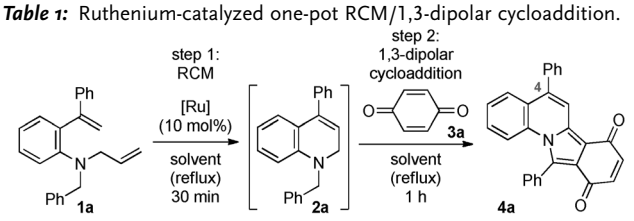
Table 1: Ruthenium-catalyzed one-pot RCM/1,3-dipolar cycloaddition.



Entry	[Ru]	Solvent[a]	**3a** [equiv]	Yield of **4a** [%][b,c]
1	**B**	benzene	2	39
2	**B**	benzene	3	67
3	**B**	benzene	4	82
4	**B**	benzene	5	86
5	**B**	benzene	10	95
6	**B**	toluene	2	35
7	**B**	toluene	10	82 (84)
8	**A**	benzene	10	12
9	**C**	benzene	10	13
10	**D**	benzene	10	90

[a] The same solvent was used in steps 1 and 2. [b] According to TLC analysis, **1a** was completely converted to **2a**. [c] Yield in parenthesis: both steps performed at 80 °C.

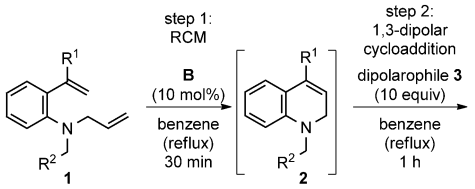
the resulting **2a** was treated without purification with two equivalents of 1,4-benzoquinone **3a**, the desired 1,3-dipolar cycloaddition product **4a** was formed in 39 % yield (Table 1, entry 1). This preliminary study showed that the proposed catalytic cascade of **1a** was indeed possible to afford **4a**, probably via the proposed azomethine ylide intermediate. Increasing the number of equivalents of **3a** afforded the product in increased yield (Table 1, entries 1–5). When ten equivalents of **3a** were used, **4a** was isolated in 95 % yield (Table 1, entry 5).[17,18] Moderate to good yields of **4a** were obtained with toluene as the solvent (Table 1, entries 6 and 7). The structure of compound **4a** was determined by single-crystal X-ray diffraction (see Figure S1 in the Supporting Information).[19]

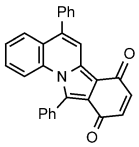
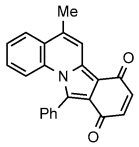
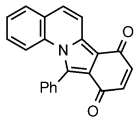
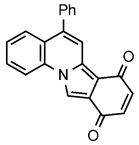
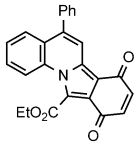
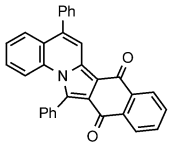
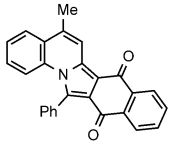
Experiments to probe the substrate scope of the tandem reaction are summarized in Table 2. Substituents on the nitrogen atom or at the α position of the styrene were not limited to phenyl, and differently substituted products were obtained in 15, 51, 32, and 45 % yield (Table 2, entries 2–5, respectively). Furthermore, in addition to 1,4-benzoquinone, 1,4-naphthoquinone and 1,2-naphthoquinone could also be used as 1,3-dipolarophiles in this reaction (Table 2, entries 6–8).

Although the core structure in these compounds was the same novel isoindolo[2,1-a]quinolone system, these compounds showed a variety colors, including blue, yellow, orange, and red (Figure 2). Hence, the absorption and emission profiles of compounds **4a–h** were investigated (see Figures 3 and 4, and Figures S2–S4 in the Supporting Information).

The isoindolo[2,1-a]quinolines **4b** and **4h**, which bear a methyl substituent at position 4 of the quinolone, clearly display absorption peaks in the near-infrared region with a maximum at 657–720 nm, and the other compounds display absorption peaks with a maximum at 447–480 nm (Figures S2–S4). Figures 3 and 4, and Figures S5 and S6 in the

Table 2: Scope of ruthenium-catalyzed one-pot RCM/1,3-dipolar cycloaddition.



Entry	**1**	R^1	R^2	**3**	**4**		Yield [%][b,c]
1	**1a**	Ph	Ph	**3a**	**4a**:		95 (84)
2	**1b**	Me	Ph	**3a**	**4b**:		15
3	**1c**	H	Ph	**3a**	**4c**:		51 (34)
4	**1d**	Ph	H	**3a**	**4d**:		32
5	**1e**	Ph	CO_2Et	**3a**	**4e**:		45 (64)
6	**1a**	Ph	Ph	**3b**	**4f**:		79
7	**1b**	Me	Ph	**3b**	**4h**:		11 (9)

[a] The same solvent was used in steps 1 and 2. [b] According to TLC analysis, **1** was completely converted to **2**. [c] Yields in parenthesis: both steps performed in toluene at 80 °C. Dienophiles: **3a** = 1,4-benzoquinone, **3b** = 1,4-naphthoquinone.

Supporting Information show the fluorescence properties of **4a–h**. The characteristic fluorescence signals of compounds **4** were observed from 540 to 620 nm in chloroform. We found that **4a–h** exhibited fluorescent emissions, and studied the emission of **4a** in several different solvents (Figure 4). Notably, these studies of **4a–h** provide the first direct experimental evidence that the isoindolo[2,1-*a*]quinoline skeleton is a fluorescent chromophore.

Interestingly, the fluorescence emission enhanced in hydrophobic solvents, such as chloroform or benzene, com-

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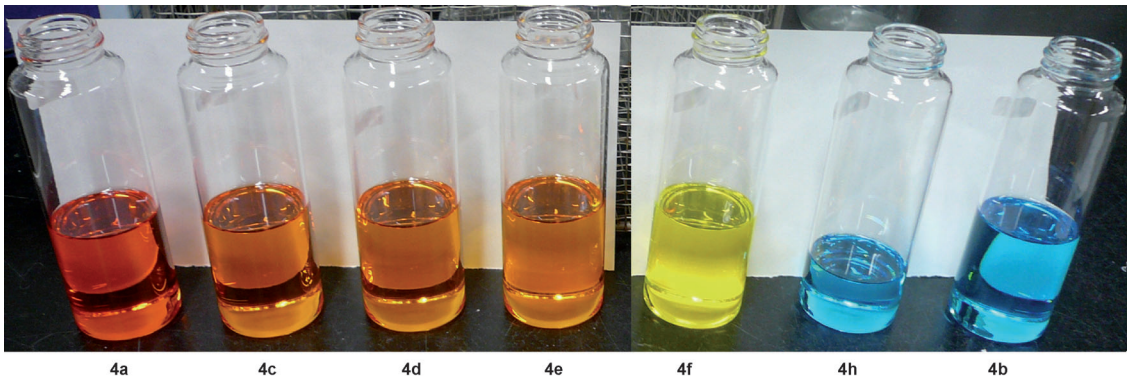

Figure 2. Colors of compounds **4** (solubilized in benzene, 100 μM).

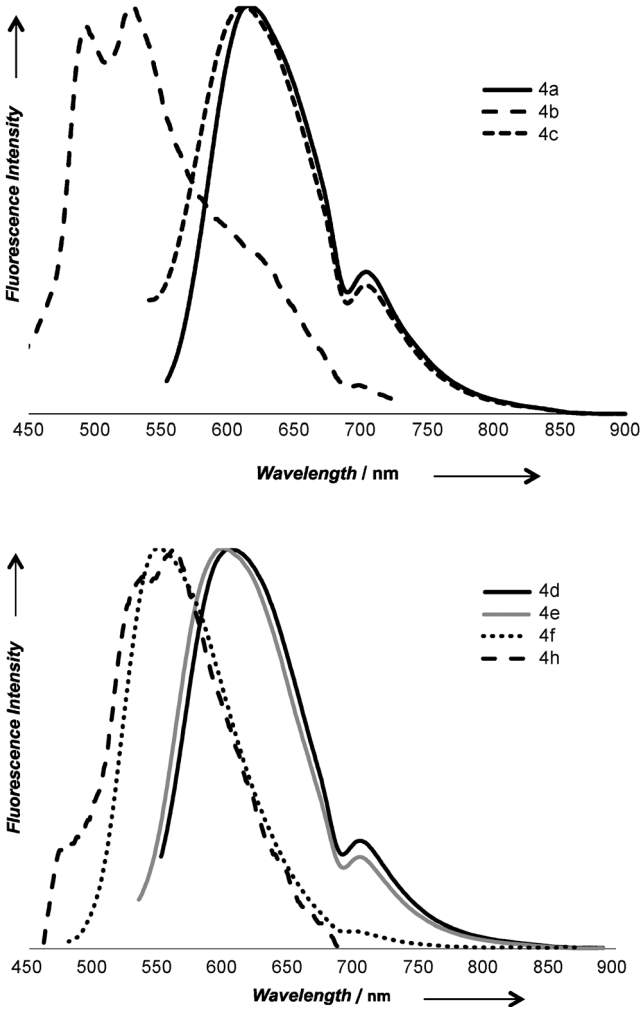

Figure 3. Fluorescence spectra of compounds **4** in chloroform.
4a: 50 μM, $\lambda_{ex}=494$ nm, $F_{max}=617$ nm, $\varphi=0.017187$, $\tau_f=0.61$ ns;
4b: 50 μM, $\lambda_{ex}=402$ nm, $F_{max}=529$ nm, $\varphi=0.000804$, $\tau_f=0.024$ ns;
4c: 50 μM, $\lambda_{ex}=476$ nm, $F_{max}=612$ nm, $\varphi=0.011698$, $\tau_f=0.60$ ns;
4d: 50 μM, $\lambda_{ex}=476$ nm, $F_{max}=604$ nm, $\varphi=0.018709$, $\tau_f=0.52$ ns;
4e: 50 μM, $\lambda_{ex}=471$ nm, $F_{max}=598$ nm, $\varphi=0.030312$, $\tau_f=0.39$ ns;
4f: 50 μM, $\lambda_{ex}=452$ nm, $F_{max}=549$ nm, $\varphi=0.469622$, $\tau_f=3.55$ ns;
4h: 50 μM, $\lambda_{ex}=419$ nm, $F_{max}=562$ nm, $\varphi=0.000568$, $\tau_f=0.13$ ns.

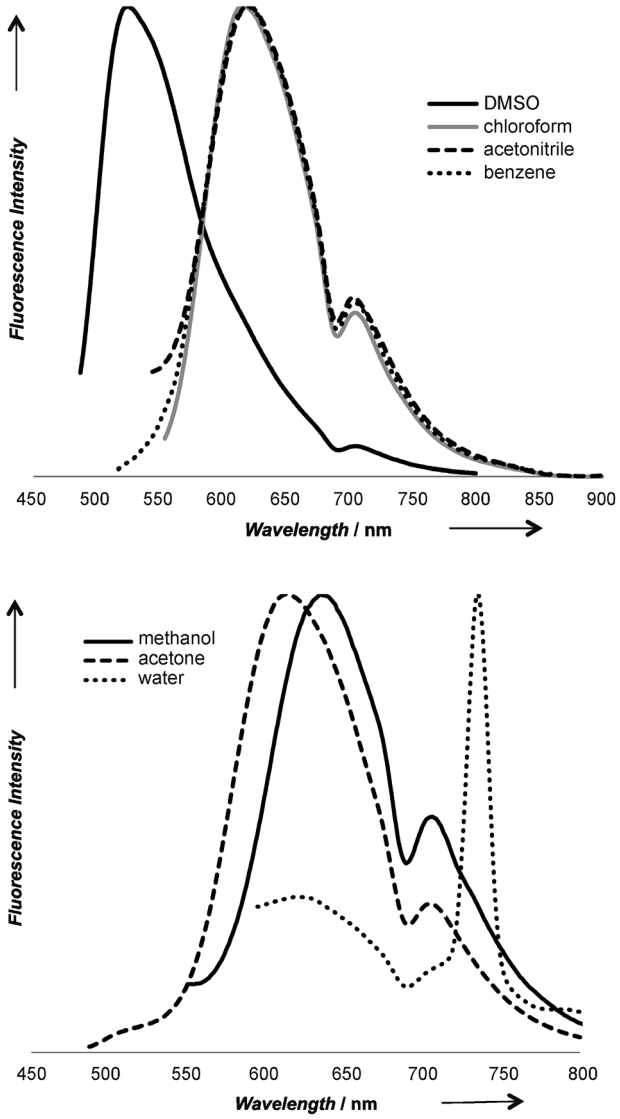

Figure 4. Fluorescence spectra of **4a** in various solvents.
DMSO: 50 μM, $\lambda_{ex}=474$ nm, $F_{max}=524$ nm, $\varphi=0.169758$;
chloroform: 50 μM, $\lambda_{ex}=494$ nm, $F_{max}=617$ nm, $\varphi=0.017187$;
acetonitrile: 50 μM, $\lambda_{ex}=477$ nm, $F_{max}=621$ nm, $\varphi=0.009385$;
benzene: 50 μM, $\lambda_{ex}=480$ nm, $F_{max}=618$ nm, $\varphi=0.015255$;
methanol: 50 μM, $\lambda_{ex}=484$ nm, $F_{max}=634$ nm, $\varphi=0.002867$;
acetone: 50 μM, $\lambda_{ex}=473$ nm, $F_{max}=613$ nm, $\varphi=0.011969$;
water: 50 μM, $\lambda_{ex}=493$ nm, $F_{max}=621$, 735 nm, $\varphi=0.002309$.

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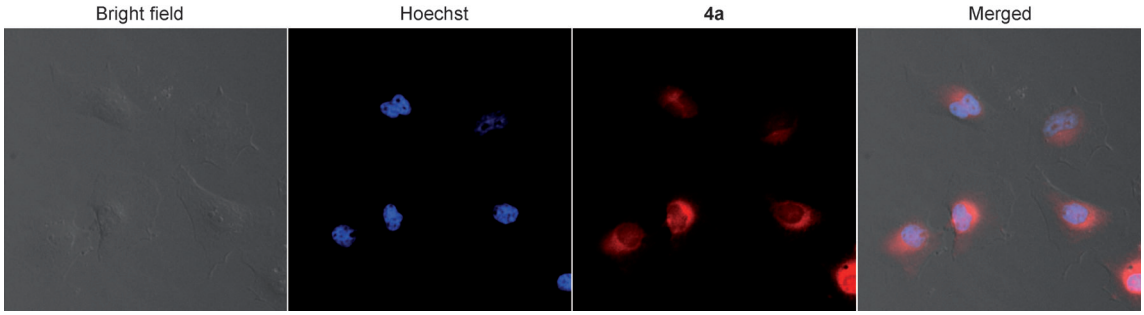

Figure 5. Fluorescence imaging of HeLa cells with probe **4a**. HeLa cells were incubated with **4a** (60 μM solution in Dulbecco's Modified Eagle Medium with 3% DMSO as cosolvent) for 30 min at 37°C. Cells were fixed with formaldehyde (4%) for 15 min at room temperature, and treated with Hoechst 33342 (1 μg mL^{-1}) for 10 min at room temperature to stain the DNA in the nuclei.

pared with hydrophilic solvents, such as water. This property could be useful in sensing or imaging applications. Therefore, we carried out investigations on cellular imaging using compound **4a** (Figure 5). HeLa cells were incubated with probe **4a** (60 μM solution in Dulbecco's Modified Eagle Medium with 3% DMSO as cosolvent) for 30 min, treated with Hoechst 33342, which stains DNA in nuclei, and imaged by fluorescence microscopy. The images showed that the probe penetrated through the cell membrane and emitted a fluorescence signal. Figure 5 shows that the probe was mainly localized in and around the nucleus and provided a strong fluorescence signal. These findings suggest that compounds **4** can potentially be applied as fluorescent probes.

In summary, we demonstrated that the ruthenium–alkylidene catalyst **B** can be converted in situ into a catalyst that affects a 1,3-dipolar cycloaddition by treatment with an 1,3-dipolarophile.[18] The obtained isoindolo[2,1-*a*]quinoline skeleton is a novel fluorescent chromophore.

Received: August 21, 2012
Revised: October 6, 2012
Published online: November 29, 2012

Keywords: cycloaddition · domino reactions · dyes/pigments · metathesis · ruthenium

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[16] According to TLC analysis and ^{1}H NMR spectroscopy, this reaction proceeded quantitatively.
[17] According to TLC analysis and ^{1}H NMR spectroscopy, the first step (RCM) proceeded quantitatively, no matter what ruthenium catalyst **A**–**D** was employed. Although we investigated other reaction conditions by changing catalyst, solvent, temperature, number of equivalents of the 1,3-dipolarophile, ect., the yields of compounds **4**, with exception of **4a** and **4f**, were still rather low. The control experiment, which included the removal of the ruthenium species between steps 1 and 2 by column chromatography on silica gel was very difficult because of the instability of the 1,2-dihydroquinoline intermediate and the wide polarity range of the ruthenium species.
[18] An alternative scenario is that after the ruthenium-catalyzed RCM, a non-ruthenium-catalyzed oxidation of the RCM product by the excess amount of quinone generates the reactive dipolarophile, which then traps a second quinone, again in a noncatalytic fashion. A third equivalent of the quinone would

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then be required to further oxidize the direct cycloadducts to the observed product. According to TLC analyses of the experiments shown in Table 1, entries 5 and 8–10, **1a** was completely converted to **2a** in all cases, irrespective of the ruthenium catalyst that was used. However, the yield of **4a** depended dramatically on the nature of the ruthenium catalyst (with or without NHC ligand). Therefore, we consider that the ruthenium species derived from the original ruthenium–carbene catalyst plays an important role in the generation of compound **4a** during the second step of the reaction.

[19] CCDC 897064 (**1a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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