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Synthetic Methods

Development of an Enyne Metathesis/Isomerization/Diels–Alder One-Pot Reaction for the Synthesis of a Novel Near-Infrared (NIR) Dye Core

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Abstract: *N*-Alkyl-*N*-allyl-2-alkynylaniline derivatives undergo a tandem ring-closing enyne metathesis/isomerization/Diels–Alder cycloaddition sequence in the presence of a second-generation Grubbs catalyst and dienophiles. In practice, the acyclic enyne in the presence of the ruthenium alkylidene first undergoes ring-closing metathesis to generate cyclic 4-vinyl-1,2-dihydroquinolines; following diene isomerization and then the addition of a dienophile, these ring-closing metathesis products are selectively converted into a 7-methyl-4*H*-naphtho[3,2,1-*de*]quinoline-8,11-dione core. Overall, the reaction sequence converts simple aniline derivatives into π-conjugated small molecules, which have characteristic absorption in the near-infrared region, in a single operation through three unique ruthenium-catalyzed transformations.

Introduction

New applications have recently sparked interest in near-infrared (NIR) dyes, and strong NIR absorption and fluorescence emission are important and useful phenomena. Whereas fluorescence is especially applicable for labeling purposes in microscopy,[1] organic molecules with eminent NIR absorption have attracted much interest because of the wide range of applications of their optical and electronic properties.[2,3] NIR-emitting molecules are even more appealing. Their applications include night vision, optical communication, bioimaging, and sensing, among others.[4,5] NIR-active molecules with minimal UV/Vis absorption are useful for transparent photovoltaics, heat-block coating, optical filters, and information-security displays.[6]

The range of reported NIR dye molecular skeletons is, however, limited and the development of a novel NIR dye core structure is highly desired. Olefin metathesis of a ruthenium carbene catalyst (Figure 1) is a versatile carbon–carbon double bond-forming reaction that is widely used to prepare complex organic compounds.[7] Several reaction sequences comprising an olefin metathesis step and subsequent nonmetathesis transformation[8] of the newly generated carbon–carbon double bond have been developed. For example, by conversion of a Ru-carbene into a Ru-hydride in situ (Figure 1),[9] olefin metathesis can be coupled with hydrogenation[10] or isomerization.[11] The tandem transformations catalyzed by ruthenium alkylidenes developed to date include olefin metathesis, followed by cyclopropanation,[12] hydrovinylation,[13] hydroarylation,[14] the aza-Michael reaction,[15] the hetero-Pauson-Khand reaction,[16] or oxidation.[17]

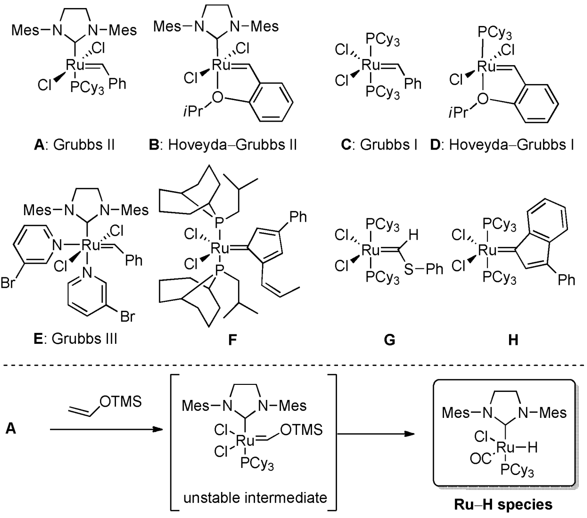

Figure 1. Ruthenium carbene catalysts.

In our search for novel and efficient Ru-catalyzed reactions,[8c,9,17d,18] we developed a one-pot ring-closing metathesis/oxidation and a one-pot ring-closing metathesis/1,3-dipolar cycloaddition to produce various 2-quinolones and isoindoloquinolines (Scheme 1), respectively, from *N*-allyl-2-alkynylaniline derivatives.[17d,18] Considering the importance of streamlining syntheses toward complex molecular targets, we describe

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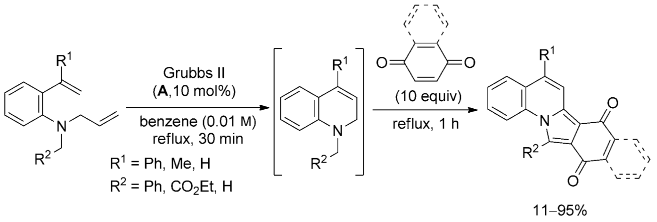
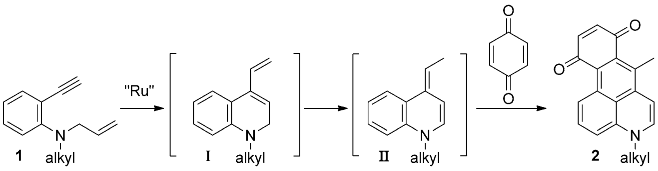


Scheme 1. Our previous work: ring-closing metathesis/1,3-dipolar cycloaddition one-pot reaction.

herein our novel one-pot metathesis/nonmetathesis process; that is, a one-pot enyne metathesis/isomerization/Diels–Alder reaction, to give 7-methyl-4*H*-naphtho[3,2,1-*de*]quinoline-8,11-dione derivatives, which are novel NIR dyes.

We envisioned the development of a one-pot enyne metathesis/isomerization/Diels–Alder reaction by using *N*-allyl-2-alkynylaniline derivatives **1** (Scheme 2), which could lead to a new solution-processable π-conjugated nitrogen-containing heterocycle, 7-methyl-4*H*-naphtho[3,2,1-*de*]quinoline.



Scheme 2. This work: enyne metathesis/isomerization/[4+2] cycloaddition one-pot reaction.

Results and Discussion

In ^{1}H NMR experiments, the *N*-allyl-*N*-benzyl-2-ethynylaniline derivative **1a** was first treated with 10 mol% **A** in [D$_6$]benzene at 50 °C for 30 min to form the corresponding 1,2-dihydoroquinoline derivative **I**. When the resulting **I** was further treated at 60 °C for 1 h, the desired isomerized product **II** was formed (Figure 2). Encouraged by these results, we continued our experiments to establish an eyene metathesis/isomerization/[4+2] cycloaddition one-pot reaction.

After treatment of **1a** with 10 mol% **A** in refluxing benzene for 10 min, the corresponding compound **II** formed, which, without purification, was treated with 5 equivalents of 1,4-benzoquinone to form the desired Diels–Alder cycloaddition product **2a** in as blue crystals in 13% yield (Table 1, entry 1). The crystal structure of novel compound **2a** was determined by single-crystal X-ray diffraction methods and found to be composed of four essentially planar rings (Figure 3).[19] This preliminary study revealed that the proposed catalytic cascade of **1a** afforded **2a** via the proposed diene intermediate **II**.[20]

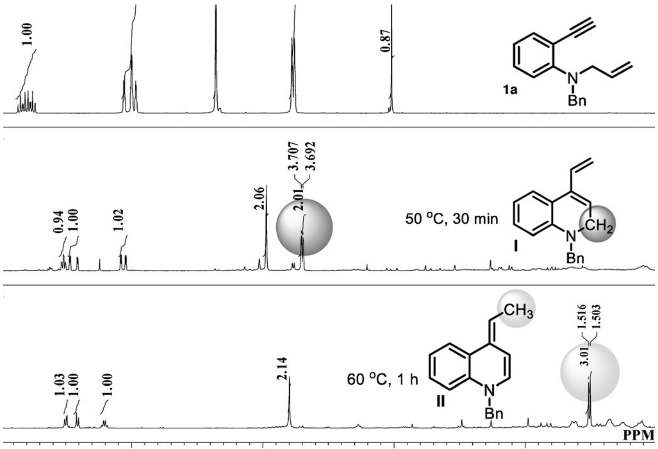
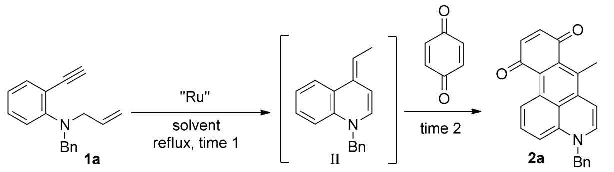


Figure 2. ^{1}H NMR spectroscopic analysis of **1a** (10 mg) and Grubbs II (**A**, 10 mol%) in C_6D_6 (0.75 mL).

Through optimization of Time 1, Time 2, the number of equivalents of 1,4-benzoquinone, and solvent concentration (Table 1), we found that the reaction conditions given in entry 8 was optimal. A 47% yield of **2a** was obtained with tetrahydrofuran (THF) as a solvent (entries 8–12). Of ruthenium carbene catalysts **A**–**H** (Figure 1), only reactions using catalyst **B** and **D** gave **2a** in 5 and 24% yields (entries 13 and 14), respectively, probably due to the activity of Ru catalysts on isomerization. When, as a control experiment, isolated compound **I** was heated in benzene at 60 °C for 1 h under the conditions shown in Figure 2, only unreacted **I** was observed. This result suggests that the isomerization is Ru-catalyzed. Based on the

Table 1. Optimization of enyne metathesis/isomerization/[4+2] cycloaddition one-pot reaction.



Entry	"Ru" ([mol%])	Solvent ([M])	Time 1 [min]	Benzoquinone [equiv]	Time 2 [min]	Yield of **2a** [%]
1	**A** (10)	benzene (0.01)	10	5	10	13
2	**A** (10)	benzene (0.01)	60	5	10	18
3	**A** (10)	benzene (0.01)	60	5	60	33
4	**A** (10)	benzene (0.01)	60	5	120	31
5	**A** (10)	benzene (0.01)	60	10	60	32
6	**A** (10)	benzene (0.01)	60	3	60	15
7	**A** (10)	benzene (0.1)	60	5	60	6
8	**A** (10)	benzene (0.005)	60	5	60	38
9	**A** (10)	toluene (0.005)	60	5	60	22
10	**A** (10)	$ClCH_2CH_2Cl$ (0.005)	60	5	60	9
11	**A** (10)	THF (0.005)	60	5	60	47
12	**A** (10)	1,4-dioxane (0.005)	60	5	60	46
13	**B** (10)	THF (0.005)	60	5	60	3
14	**E** (10)	THF (0.005)	60	5	60	24
15	**A** (5)	THF (0.005)	60	5	60	3
16	**A** (20)	THF (0.005)	60	5	60	34

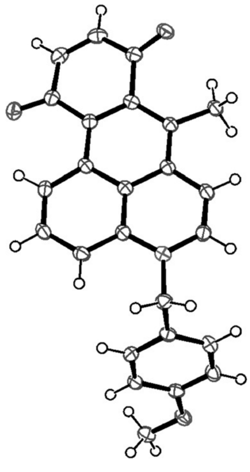
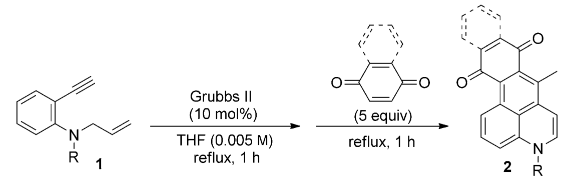


Figure 3. X-ray structure of **2a**.

results of the experiments shown in entries 11, 15, and 16, it was concluded that 10 mol% **A** was necessary to produce **2a** in better yield.

Experiments to probe the substrate scope of the reaction are summarized in Table 2. Substituents on the nitrogen, which might influence the NIR absorption or fluorescence and will be discussed below, were not limited to benzyl, and these derivatives afforded the corresponding products in 16, 65, 37, and 27% yields, respectively (entries 2–5). However, there seems to be an electronic effect in this reaction; a bromobenzyl substituent or a 4-methoxybenzyl substituent, with electron-withdrawing or electron-releasing group, respectively, gave less or more corresponding product, respectively. The *N*-toluenesulfonyl derivative was not converted into the corresponding tetracyclic compound, because subsequent isomerization of the generated 1,2-dihydroquinoline was problematic. Furthermore, not only 1,4-benzoquinone, but also 1,4-naphthoquinone worked as a dienophile (entries 6–7) in this reaction.

Table 2. Enyne metathesis/isomerization/[4+2] cycloaddition one-pot reaction; substituent effect on nitrogen.



Entry	Substrate **1**	R	Dienophile [5 equiv]	Yield of **2** [%]
1	**1a**	C_6H_5-CH_2	1,4-benzoquinone	**2a** (47)
2	**1b**	4-Br-C_6H_4-CH_2	1,4-benzoquinone	**2b** (16)
3	**1c**	4-MeO-C_6H_4-CH_2	1,4-benzoquinone	**2c** (65)
4	**1d**	3,4-diMeO-C_6H_3-CH_2	1,4-benzoquinone	**2d** (37)
5	**1e**	3,4,5-triMeO-C_6H_2-CH_2	1,4-benzoquinone	**2e** (27)
6	**1a**	C_6H_5-CH_2	1,4-naphthoquinone	**2f** (32)
7	**1c**	4-MeO-C_6H_4-CH_2	1,4-naphthoquinone	**2g** (34)

Given that all compounds of type **2** were blue solids, we then investigated the absorption and emission profile of **2a**–**c** and **2f**, as shown in Figures 4, 5, 6, and 7. Compound **2a** showed similar absorption spectra in all the solvents investigated (Figure 4). The fluorescence intensity of **2a** was higher in MeOH or dimethyl sulfoxide (DMSO) (Figure 5). Compounds **2a**–**c** and **2f** displayed clear absorption peaks in the NIR, with a maximum at 675–730 nm in all solvents examined (Figure 4 and Figure 6). The fluorescent properties of **2a**–**c** and **2f** are shown in Figure 5 and Figure 7. The characteristic fluorescent absorption bands of **2a**–**c** were observed from 471 to 472 nm

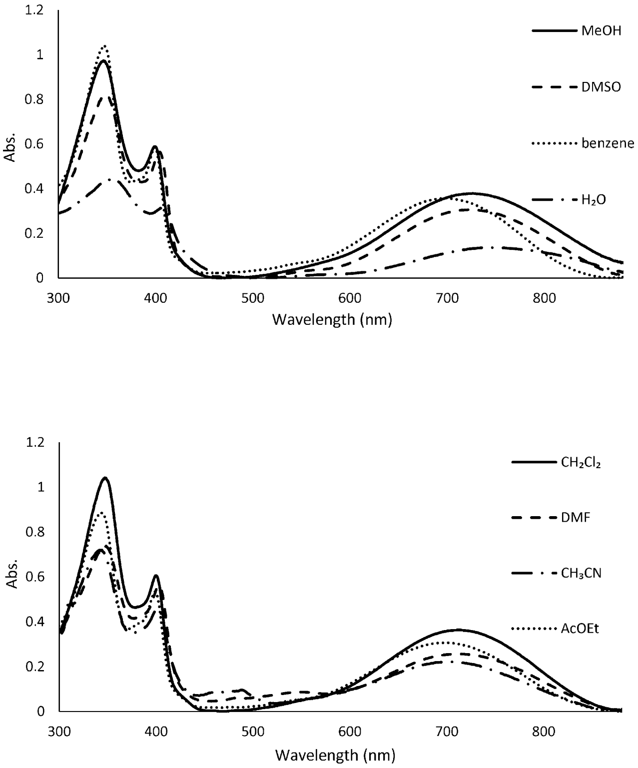


Figure 4. Absorption spectrum of **2a**.

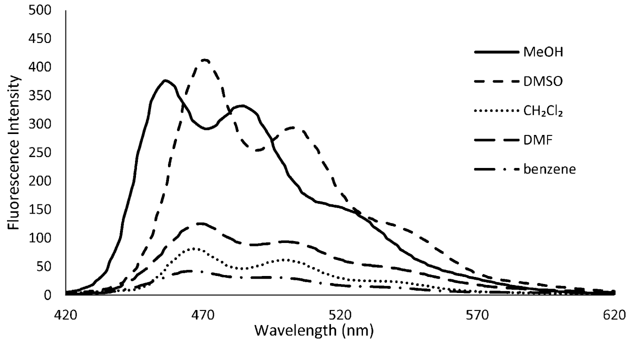


Figure 5. Fluorescence spectrum of **2a** (420–620 nm).

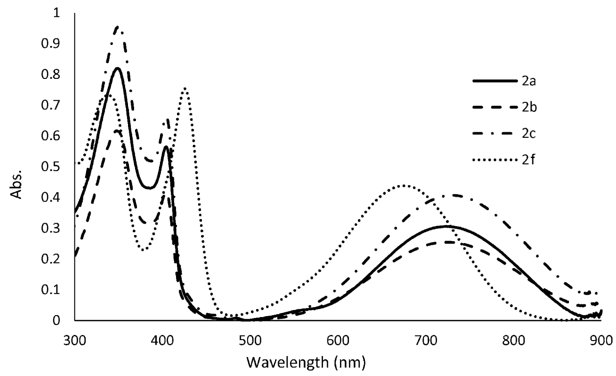


Figure 6. Absorption spectrum of **2a**–**c** and **2f** in DMSO.

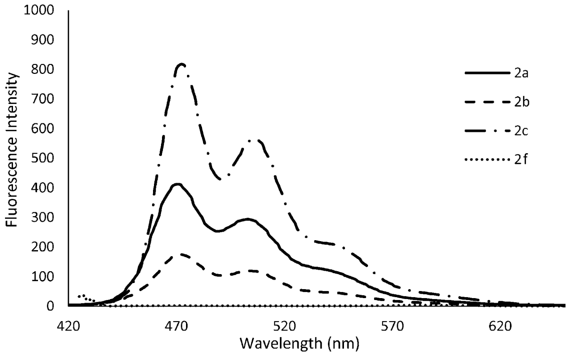


Figure 7. Fluorescence spectrum of **2 a**–**c** and **2 f** in DMSO.

in DMSO. These results are important because these frameworks add another NIR structural moiety to the repertoire of practical NIR dye cores that are available for development.

Conclusion

We report the first example of a ring-closing enyne metathesis/isomerization/Diels–Alder cycloaddition sequence in the presence of a second-generation Grubbs catalyst and dienophiles. The obtained 7-methyl-4*H*-naphtho[3,2,1-*de*]quinoline-8,11-dione core is a novel NIR absorption dye.

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

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[19] CCDC 1060726 (**2 a**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

[20] Although the yields are low to moderate, we could not observe recovered **I** and/or **II**, nor were we able to isolate any by-products. It seems that the Diels–Alder reaction step in the sequence is problematic, because enyne metathesis and isomerization steps proceeded without the formation of any by-products (Figure 2).

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