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A Fluorescence-Based High-Throughput Screening Method for Olefin Metathesis Using a Ratiometric Fluorescent Probe

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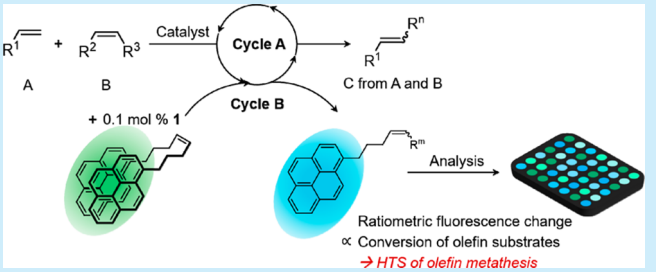
Supporting Information

ABSTRACT: (*Z*)-1,8-Di(pyren-1-yl)oct-4-ene (**1**) was prepared as a probe for olefin metathesis. The conversions of substrate by olefin metathesis under various conditions were calculated using the ratiometric fluorescence intensity change of **1**. The conversions calculated by **1** and gas chromatography were consistent. These results show that conversions of olefin metathesis can be simply obtained from the fluorescence change of **1** and this method can be applied to the high-throughput screening (HTS) method for various olefin metathesis.



Over the past decades, olefin metathesis, rearranging two carbon−carbon double bonds,[1] has emerged as one of the most attractive and powerful tools in various synthetic fields, involving polymers, natural products, pharmaceuticals, and organic synthesis.[2] However, olefin metathesis catalysts developed earlier had various limitations including sensitivity to air and moisture.[3] To overcome these limitations, a number of catalysts have been developed using complexes of ligands and transition metals.[4] Among them, commercially available ruthenium-based catalysts like Grubbs catalyst I (**G-I**), Grubbs catalyst II (**G-II**), Grubbs catalyst III (**G-III**), Hoveyda−Grubbs catalyst I (**HG-I**), and Hoveyda−Grubbs catalyst II (**HG-II**) are representative olefin metathesis catalysts. Although these catalysts exhibit outstanding catalytic reactivity and stability, there are still demands for the development of eco-friendly, cost-effective, and air- and moisture-stable olefin metathesis catalysts. Therefore, there have been several attempts to develop more efficient olefin metathesis catalysts and reaction conditions.[5]

Development of an efficient catalytic system consists of numerous elements, including ligands, metals, temperature, solvents, and additives. These numerous considerations require many development processes and lead to a waste of human and material resources. To address these issues, high-throughput screening (HTS) methods, which were originally used for enhancing the efficiency of drug discovery in the pharmaceutical industry,[6] have been applied to the development of an efficient catalytic system. These methods facilitated analysis to optimize the catalytic system. Because of the advantage of the HTS method, various technologies, such as high-performance liquid chromatography (HPLC),[7] gas chromatography (GC),[8] nuclear magnetic resonance (NMR),[9] and mass spectrometry (MS),[10] have been used as HTS methods for developing a catalytic system. However, these protocols have some drawbacks, primarily the high cost of the instrument and the long analysis time per sample. To overcome these drawbacks, HTS methods using colorimetric[11] and fluorometric assays[12] have been developed. The instruments required for these assays are relatively inexpensive, with short analysis times. Fluorescence-based HTS methods have attracted considerable attention because of their high sensitivity and easy sample preparation. Despite its importance of olefin metathesis, only one fluorescence-based HTS method for olefin metathesis has been developed thus far. In 2015, Reuter et al. reported a profluorescent substrate based HTS method[13] that can be used to measure the catalytic efficiency of only ring-closing metathesis (RCM), one class of olefin metathesis, because the fluorescence of the profluoroscent substrate was induced through RCM. Therefore, this method has a critical limitation because it cannot be applied to other olefin metatheses or other substrates. Previously, our group developed some of HTS methods for catalytic organic reactions using an optical chemosensor system to screen various reaction conditions including additives, substrates, solvents, and temperature.[14] The activity of the catalyst was easily analyzed based on optical changes, and the values obtained correlated well with those obtained by GC analysis. Therefore, we thought that these strategies would be a solution for the limitations found in the previous HTS method.

In this study, a fluorescence-based HTS method for olefin metathesis was developed using fluorescent probe (*Z*)-1,8-di(pyren-1-yl)oct-4-ene (**1**), which contained a *Z*-olefin as the reaction site and two pyrenes as the fluorophore. Pyrene has a dual fluorescence emission, depending on the distance between the two pyrenes, the monomer emission ranging from 380 to 410 nm, and the excimer emission ranging from 450 to 500 nm.[15] In addition, pyrene has high chemical stability toward various reaction conditions because it consists of only carbon

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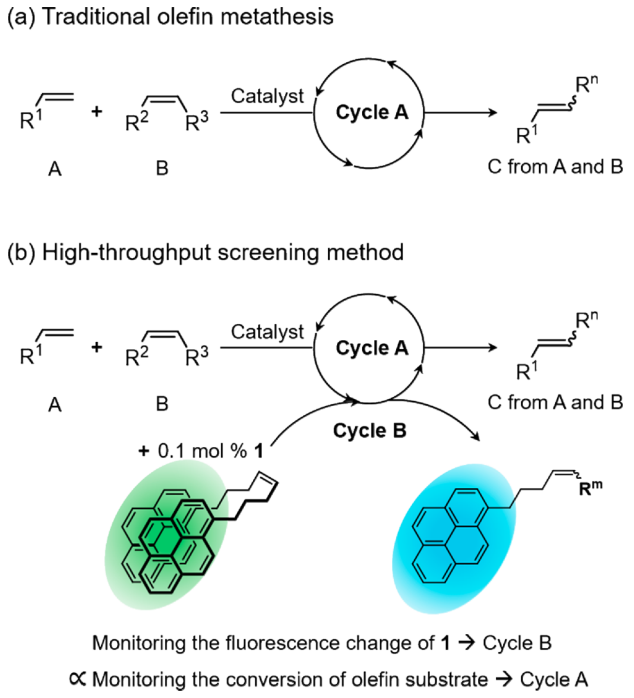
and hydrogen. The *Z*-olefin not only is the reaction site but also can induce pyrene excimer emission by conformation restriction in **1**. If the internal olefin of **1** participates in olefin metathesis, the pyrenes may be located far away from each other. Therefore, the fluorescence intensity of the excimer will decrease as olefin metathesis progresses, and the fluorescence intensity of the monomer will increase. These changes in fluorescence intensity can be used for measuring the conversions of various olefin metathesis reactions (Scheme 1).

Scheme 1. Schematic Representation of the Fluorescent Probe 1 Based High-Throughput Screening Method for Olefin Metathesis



To develop the fluorescence-based HTS method for olefin metathesis using fluorescent probe **1**, we studied the correlation between the analysis based on the fluorescence of **1** and GC analysis in olefin metathesis. The cross-metathesis (CM) reaction of allylbenzene (**5**) and *cis*-1,4-diacetoxy-2-butene (**6**) was chosen as a model reaction[16] and was carried out using **G-II** in the presence of 0.1 mol % of **1** (Figure 1). Small amounts of the reaction mixtures were collected each time during a 5 h, and ethyl vinyl ether was added to each sample to terminate the metathesis. The reaction mixtures were analyzed by both fluorescence spectrophotometer and GC. As expected, the excimer fluorescence intensity at 462 nm decreased and the monomer fluorescence intensity at 378 nm increased during the reaction (Figure 1a). These fluorescence changes, excimer to monomer, were converted to the fluorescence intensity ratio (log (I_{378}/I_{462})).[17] Using these ratiometric fluorescence intensity changes at different time intervals, the kinetic profile of fluorescence intensity ratio of the reaction mixtures versus time was obtained. The initial slope of the log (I_{378}/I_{462}) versus time graph, which is considered the reaction rate, increased with increasing amount of **G-II**. Similar to Figure 1a, GC conversion of **5** increased during the reaction and the slope of the conversion of **5** versus time graph increased with increasing amount of **G-II** (Figure 1b). Comparison of the two graphs revealed that the ratiometric fluorescence intensity change of **1** was highly correlated with the GC conversion of **5** at each time interval. Based on the correlation between the fluorescence intensity ratio and the GC conversion of **5** at each time interval, the standard curve of the conversion of **5** versus log (I_{378}/I_{462}) graph was obtained (Figure 1c). The conversion, which was calculated from this standard curve, was denoted as fluorescence conversion.

To expand the application of **1** as a chemosensor for the analysis of other CM reactions, we analyzed CM reactions between **5** and other internal olefins (*cis*-4-octene (**7**) or methyl oleate (**8**)) in the presence of 0.1 mol % of **1**. The ratiometric fluorescence intensity change of **1** of these CM reactions correlated well with their corresponding GC conversions of **5**. The standard curves for other combinations of CM reaction were in the Supporting Information (Figure S3 for **5** and **7** and S4 for **5** and **8**). In addition, to examine the influence of **1** on olefin metathesis, CM was carried out in the presence and absence of **1**. **5** was used as a terminal olefin, and three kinds of internal olefin (**6**, **7**, **8**) were used as counter olefins. The conversion of **5** was monitored at differing time points using GC. There was no difference in conversion of **5** in the presence or absence of **1**. These results show that a small amount of **1** does not affect olefin metathesis reactions (Figure S5 in the Supporting Information). Therefore, these results supported the fact that fluorescent probe **1** can determine the conversion of olefin substrates in olefin metathesis through fluorescence changes.

The activities of metathesis catalysts using **5** as the terminal olefin and three kinds of internal olefins (**6**, **7**, **8**) were then screened. The commercially available metathesis catalysts, **G-I**, **G-II**, **G-III**, **HG-I**, and **HG-II**, were used for these CM reactions. Once the reactions were completed, the conversion of **5** was analyzed by fluorescence and GC separately. As shown in Figure 2, the fluorescence conversion of **5** exhibited high correlation with the GC conversion of **5**.[18] These results indicate the following: (1) The ratiometric fluorescence intensity change of **1** in CM reactions can effectively be used to screen the activities of the catalysts. (2) The method could screen the CM reactions effectively with only 0.1 mol % of **1**. (3) The method provided information on the conversion of substrates in olefin metathesis. These important findings in our study suggest a method to overcome the drawbacks of the profluorescent substrate-based HTS method for olefin metathesis.[13]

Recently, there have been several attempts to use additives in olefin metathesis to improve the reactivity of the catalyst or to suppress the side reaction.[19] Therefore, the effects of various additives on CM reactions using the fluorescence-based HTS method were evaluated. CM was carried out using **5** and three kinds of internal olefins (**6**, **7**, **8**) as a substrate, **G-II** as catalyst, and additives in the presence of 0.1 mol % of **1**. Fourteen kinds of additives were selected, including polymers, organic bases, organic acids, carbonyls, and Lewis acids. In our experiments,[18] the efficiency of **G-II** decreased in the presence of pyridine or triethylamine in all substrates. These results were similar to the previous research that confirm a deactivation effect of amine-containing additives.[19c,f,20] On the other hand, tin(II) chloride ($SnCl_2$) increased the efficiency of **G-II** in all substrates. $SnCl_2$ is known to increase the reactivity of catalysts.[21] These results correlated well with previous results. As shown in Figure 3b, fluorescence conversion correlated well with the GC

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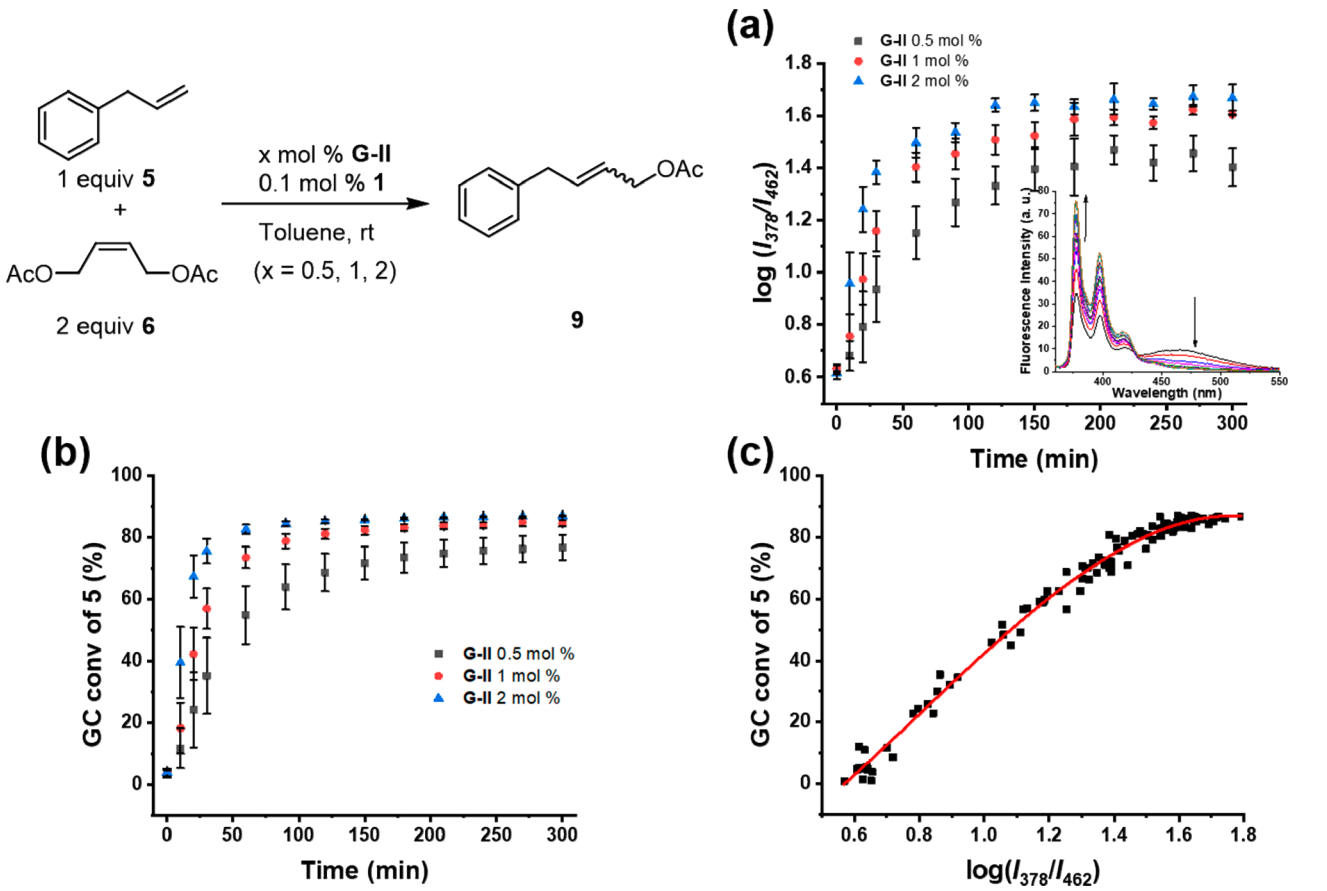

Figure 1. Schematic of the CM reaction. Reaction conditions: **5** (0.3 mmol), **6** (0.6 mmol), **G-II** (0.5−2 mol %), **1** (0.1 mol %), dodecane (0.3 mmol, internal standard), and toluene (3.0 mL) at room temperature. (a) Kinetic profile (0−300 min) of the ratiometric fluorescence intensity changes of **1** in the CM reaction at different concentrations of **G-II** (x = 0.5, 1, 2). Inset: Fluorescence spectra of **1** in the CM reaction (0−300 min, **G-II** 0.5 mol %). (b) Kinetic profile (0−300 min) of the conversion of **5** in the CM with **1** using GC at different concentrations of **G-II** (x = 0.5, 1, 2). (c) Standard curve A: GC conversion of **5** versus log (I_{378}/I_{462}).

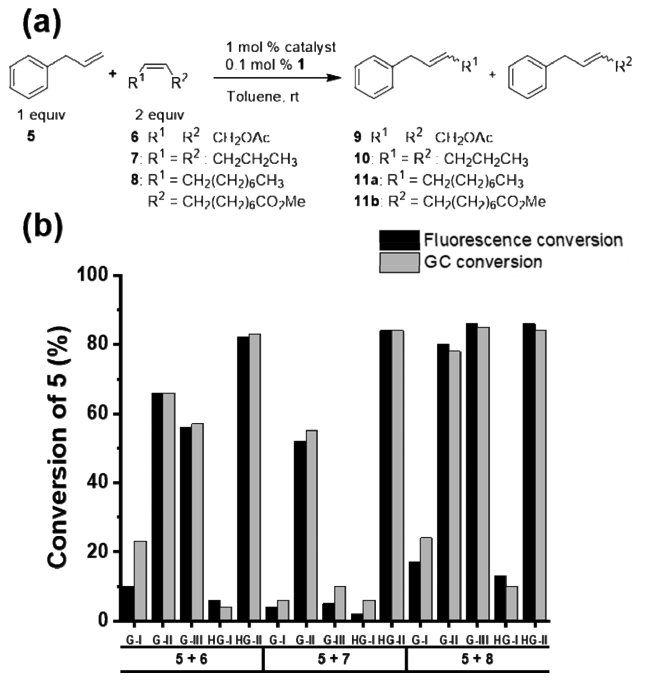

Figure 2. (a) Schematic of catalyst screening for cross-metathesis. (b) Correlation graph between the conversion of **5** by **1** and GC.

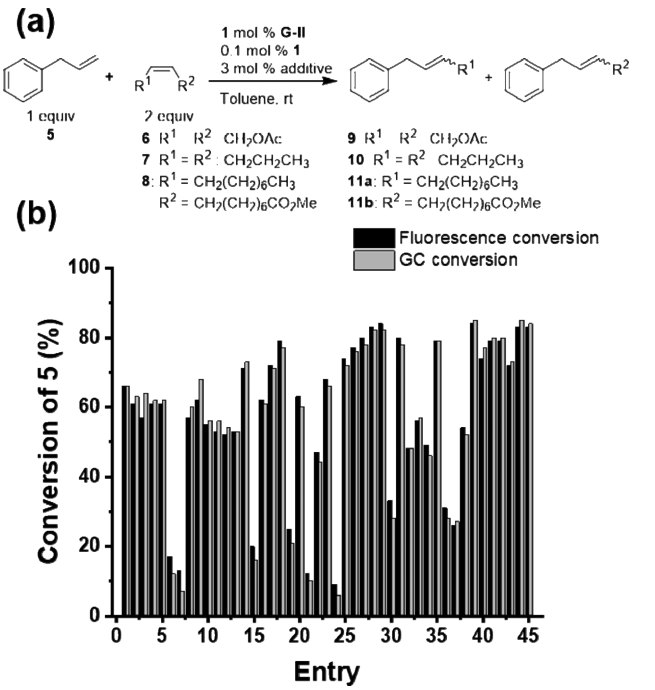

Figure 3. (a) Schematic of an additive screening for cross-metathesis. (b) Correlation graph between the conversion of **5** by **1** and GC.

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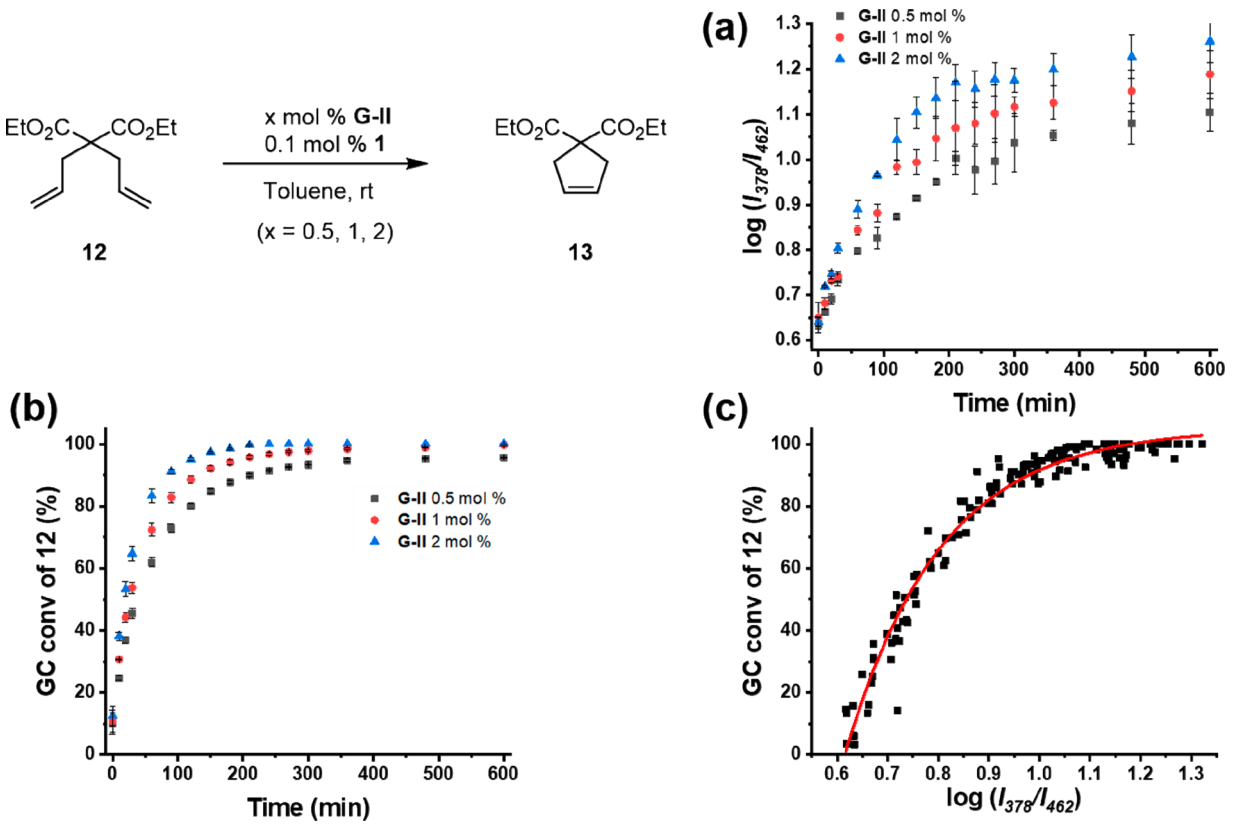

Figure 4. Reaction conditions: **12** (0.3 mmol), **G-II** (0.5−2 mol %), **1** (0.1 mol %), and toluene (3.0 mL) at room temperature. (a) Kinetic profile (0 to 600 min) of the ratiometric fluorescence intensity changes of **1** in the RCM reaction at different concentrations of **G-II** (x = 0.5, 1, 2). (b) Kinetic profile (0 to 600 min) of the conversion of **12** in the RCM with **1** using GC at different concentrations of **G-II** (x = 0.5, 1, 2). (c) Standard curve D: GC conversion of **12** versus log (I_{378}/I_{462}).

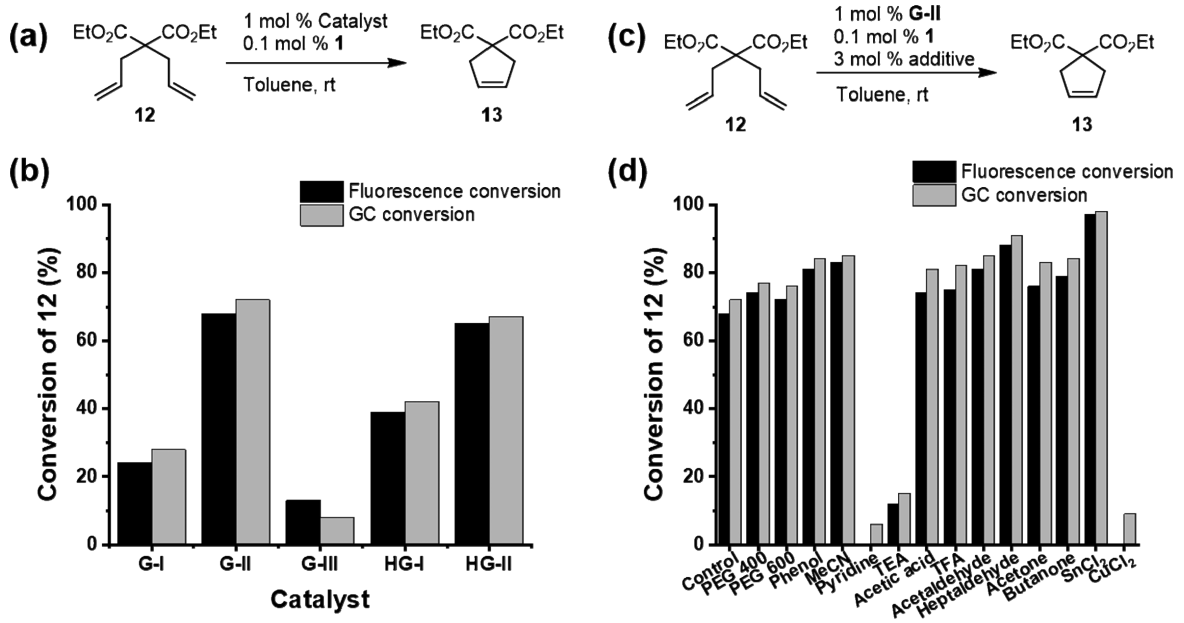

Figure 5. (a) Schematic of catalyst screening for ring-closing metathesis. (b) Correlation graph between the conversion of **12** by **1** and GC. (c) Schematic of additive screening for ring-closing metathesis. (d) Correlation graph between the conversion of **12** by **1** and GC.

conversion of **5**, with errors in the range below 7%. These results indicate that this fluorescence-based HTS method is an efficient tool for screening additives of olefin metathesis.

To examine the general application of the fluoresce-based HTS method, **1** was used in RCM, the other class of olefin metathesis. Diethyl diallylmalonate (**12**) was used as a model substrate,[16] and experiments similar to the CM reactions were carried out. Model RCM reactions were carried out using **G-II**, and the standard curve for calculating the fluorescence conversion of **12** was obtained (Figure 4).

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Using this standard curve, the screening of catalysts and additives in RCM reactions were carried out (Figure 5).[18] As shown in Figure 5, the fluorescence conversion correlated well with the GC conversions of **12**, with errors in the range below 10%. These results indicate that the fluorescence-based HTS method using **1** is an efficient screening method for not only CM in various conditions but also RCM. To the best of our knowledge, this is the first fluorescence-based HTS method.

In conclusion, a new fluorescence-based HTS method has been developed that shows high performance as a tool for screening various olefin metathesis conditions, such as olefin substrates, catalysts, and additives. One of the most important features of this fluorescence-based HTS method is that it can be applied to both cross-metathesis and ring-closing metathesis. Fluorescent probe **1** has shown to have no effect on the reactivity of the catalyst in reaction mixtures. The conversion of olefin substrates calculated by the ratiometric fluorescence intensity changes of **1** correlated well with GC. As a result, it is expected that the fluorescence-based HTS method developed in this study will be a useful tool for developing olefin metathesis catalysts and additives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04462.

Experimental procedures (preparation of **1** and screening method), Schemes S1−S4, Figures S1−S17, Tables S1−S4, and spectral data for products (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Chauvin, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3740. (b) Schrock, R. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 3748. (c) Grubbs, R. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 3760. (d) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243. (e) Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746.

(2) (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Mol, J. C. *J. Mol. Catal. A: Chem.* **2004**, *213*, 39. (c) Hoveyda, A. H.; Malcolmson, S. J.; Meek, S. J.; Zhugralin, A. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 34. (d) Nicola, T.; Brenner, M.; Donsbach, K.; Kreye, P. *Org. Process Res. Dev.* **2005**, *9*, 513. (e) Meek, S. J.; O'brien, R. V.; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *471*, 461.

(3) (a) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, *1*, 371. (b) Conrad, J. C.; Fogg, D. E. *Curr. Org. Chem.* **2006**, *10*, 185.

(4) Samojłowicz, C.; Bieniek, M.; Grela, K. *Chem. Rev.* **2009**, *109*, 3708. (b) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247. (c) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (d) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

(5) (a) Van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954. (b) Yao, Q.; Zhang, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 3395. (c) Smoleń, M.; Kędziorek, M.; Grela, K. *Catal. Commun.* **2014**, *44*, 80.

(6) Bleicher, K. H.; Böhm, H.-J.; Müller, K.; Alanine, A. I. *Nat. Rev. Drug Discovery* **2003**, *2*, 369.

(7) (a) Burgess, K.; Lim, H.-J.; Porte, A. M.; Sulikowski, G. A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 220. (b) Porte, A. M.; Reibenspies, J.; Burgess, K. *J. Am. Chem. Soc.* **1998**, *120*, 9180. (c) Cai, C.; Chung, J. Y. L.; McWilliams, J. C.; Sun, Y.; Shultz, C. S.; Palucki, M. *Org. Process Res. Dev.* **2007**, *11*, 328.

(8) (a) Uozumi, Y.; Nakai, Y. *Org. Lett.* **2002**, *4*, 2997. (b) Jiang, X.-B.; Van Leeuwen, P. W. N. M.; Reek, J. N. H. *Chem. Commun.* **2007**, 2287.

(9) Dalvit, C.; Fagerness, P. E.; Hadden, D. T. A.; Sarver, R. W.; Stockman, B. J. *J. Am. Chem. Soc.* **2003**, *125*, 7696.

(10) (a) Guo, J.; Wu, J.; Siuzdak, G.; Finn, M. G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1755. (b) Reetz, M. T.; Becker, M. H.; Klein, H.-W.; Stöckigt, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 1758. (c) Szewczyk, J. W.; Zuckerman, R. L.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 216.

(11) (a) Lavastre, O.; Morken, J. P. *Angew. Chem., Int. Ed.* **1999**, *38*, 3163. (b) Kawatsura, M.; Hartwig, J. F. *Organometallics* **2001**, *20*, 1960. (c) Löber, O.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4366. (d) Kennedy, D. F.; Messerle, B. A.; Rumble, S. L. *New J. Chem.* **2009**, *33*, 818.

(12) (a) Shaughnessy, K. H.; Kim, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 2123. (b) Stambuli, J. P.; Stauffer, S. R.; Shaughnessy, K. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 2677. (c) Stauffer, S. R.; Beare, N. A.; Stambuli, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4641. (d) Stauffer, S. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 6977. (e) Angelovski, G.; Keränen, M. D.; Linnepe, P.; Grudzielanek, S.; Eilbracht, P. *Adv. Synth. Catal.* **2006**, *348*, 1193. (f) Guo, H.-M.; Tanaka, F. *J. Org. Chem.* **2009**, *74*, 2417. (g) Xia, B.; Gerard, B.; Solano, D. M.; Wan, J.; Jones, G., II; Porco, J. A., Jr. *Org. Lett.* **2011**, *13*, 1346.

(13) Reuter, R.; Ward, T. R. *Beilstein J. Org. Chem.* **2015**, *11*, 1886.

(14) (a) Jung, E.; Kim, S.; Kim, Y.; Seo, S. H.; Lee, S. S.; Han, M. S.; Lee, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 4386. (b) Kim, S.; Jung, E.; Kim, M. J.; Pyo, A.; Palani, T.; Eom, M. S.; Han, M. S.; Lee, S. *Chem. Commun.* **2012**, *48*, 8751. (c) Pyo, A.; Kim, S.; Kumar, M. R.; Byeun, A.; Eom, M. S.; Han, M. S.; Lee, S. *Tetrahedron Lett.* **2013**, *54*, 5207. (d) Byeun, A.; Baek, K.; Han, M. S.; Lee, S. *Tetrahedron Lett.* **2013**, *54*, 6712. (e) Eom, M. S.; Noh, J.; Kim, H.-S.; Yoo, S.; Han, M. S.; Lee, S. *Org. Lett.* **2016**, *18*, 1720. (f) Kim, H.-S.; Eom, M. S.; Han, M. S.; Lee, S. *Chem. - Eur. J.* **2017**, *23*, 6282. (g) Son, Y.; Lee, S.; Kim, H.-S.; Eom, M. S.; Han, M. S.; Lee, S. *Adv. Synth. Catal.* **2018**, *360*, 3916.

(15) (a) Förster, T. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 333. (b) Winnik, F. M. *Chem. Rev.* **1993**, *93*, 587. (c) Huang, J.; Wu, Y.; Chen, Y.; Zhu, Z.; Yang, X.; Yang, C. J.; Wang, K.; Tan, W. *Angew. Chem., Int. Ed.* **2011**, *50*, 401. (d) Bains, G. K.; Kim, S. H.; Sorin, E. J.; Narayanaswami, V. *Biochemistry* **2012**, *51*, 6207. (e) Thirupathi, P.; Park, J.-Y.; Neupane, L. N.; Kishore, M. Y. L. N.; Lee, K.-H. *ACS Appl. Mater. Interfaces* **2015**, *7*, 14243.

(16) (a) Ritter, T.; Hejl, A.; Wenzel, A. G.; Funk, T. W.; Grubbs, R. H. *Organometallics* **2006**, *25*, 5740. (b) Endo, K.; Grubbs, R. H. *Dalton Trans* **2016**, *45*, 3627. (c) Ambrosio, C.; Paradiso, V.; Costabile, C.; Bertolasi, V.; Caruso, T.; Grisi, F. *Dalton Trans* **2018**, *47*, 6615.

(17) For the mechanism study, see Supporting Information.

(18) Conversion data from the olefin metathesis was presented in the Supporting Information.

(19) (a) Slugovc, C.; Demel, S.; Stelzer, F. *Chem. Commun.* **2002**, *34*, 2572. (b) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J.*

DOI: 10.1021/acs.orglett.9b04462
Org. Lett. XXXX, XXX, XXX−XXX

Am. Chem. Soc. **2005**, *127*, 17160. (c) P'Poo, S. J.; Schanz, H.-J. *J. Am. Chem. Soc.* **2007**, *129*, 14200. (d) Voigtritter, K.; Ghorai, S.; Lipshutz, B. H. *J. Org. Chem.* **2011**, *76*, 4697. (e) Kang, E.-H.; Yu, S. Y.; Lee, I. S.; Park, S. E.; Choi, T.-L. *J. Am. Chem. Soc.* **2014**, *136*, 10508. (f) Neville, A.; Iniesta, J.; Palomo, J. M. *Molecules* **2016**, *21*, 1680.

(20) (a) Lummiss, J. A. M.; Ireland, B. J.; Sommers, J. M.; Fogg, D. E. *ChemCatChem* **2014**, *6*, 459. (b) Ireland, B. J.; Dobigny, B. T.; Fogg, D. E. *ACS Catal.* **2015**, *5*, 4690.

(21) Meyer, W. H.; McConnell, A. E.; Forman, G. S.; Dwyer, C. L.; Kirk, M. M.; Ngidi, E. L.; Blignaut, A.; Saku, D.; Slawin, A. M. Z. *Inorg. Chim. Acta* **2006**, *359*, 2910.

DOI: 10.1021/acs.orglett.9b04462
Org. Lett. XXXX, XXX, XXX−XXX