Streamlined construction of a natural product framework

Nature makes biologically active organic molecules bearing complex polycyclic frameworks equipped with functional groups so efficiently from simple starting materials. For example, arylnaphthalide lignan natural products derived from plants, such as diphyllin, justicidin A, taiwanin E, and neojusticidin A, have diverse biological activities, including antiplat, anti-inflammatory, antiviral, and cytotoxic activities.

Fig. 1. Arylnaphthalide ligan natural products and common structural motif.

All these significant molecules has a common structural motif: 9-phenyl-1,3-dihydronaphtho[2,3-c]furan-4-ol. Therefore, the development of an efficient process that enables a short-step assembly of this polycyclic motif from simple acyclic starting materials has been an important subject in organic chemistry.
We envisioned that a transition-metal (TM)-catalyzed carboxylative cyclization and a photopromoted oxidative aromatization can be integrated into a single sequential process to realize the streamlined assembly of arylnathalenes from readily available 1,7-diaryl-1,6-diynes. Actually, various fused 4-phenylnaphthalene-1-yl carboxylates were synthesized in two steps using a ruthenium-catalyzed hydrocarboxylative cyclization of 1,7-diaryl-1,6-diynes with carboxylic acids and subsequent oxidative photocyclization. The key to success of this integral process is the stereoselective formation of exocyclic 1,3-dienyl ester intermediates via the ruthenium-catalyzed reaction.

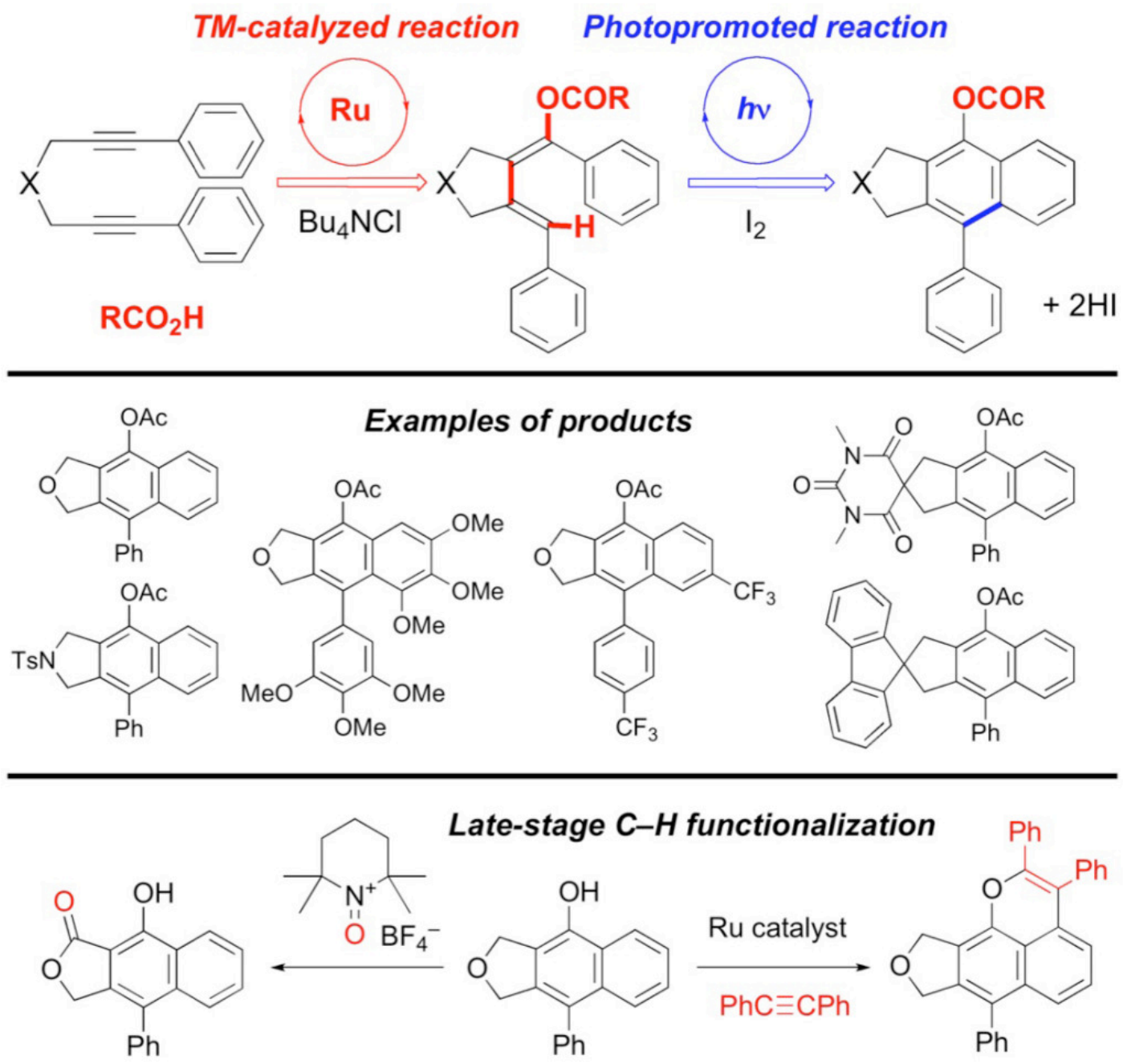

Fig. 2. Integrated transition-metal-catalyzed and photopromoted process.

Based on our previous analysis of the mechanism by DFT calculations, we successfully achieved the optimal reaction conditions using tetrabutylammonium chloride as an additive that suppresses the undesired dissociation of the chloride ligand from the ruthenium catalyst. In addition, we demonstrated that the diversification of the arylnaphthalene product is also possible using late-

stage C–H functionalization reactions, such as C–H oxidation and C–H alkenylation. As such, arylnaphthalides and 8,10-dihydrobenzo[de]furo[3,4-h]chromene were obtained. the library of natural-product-like molecules. Thus TM-catalyzed and photopromoted integrated process would open a way to develop a novel natural-product-like molecular library for drug discovery.

Yoshihiko Yamamoto
Department of Basic Medicinal Sciences, Graduate School of Pharmaceutical Sciences, Nagoya University, Chikusa, Nagoya, Japan

Publication

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