Cross-metathesis–based approaches to heteroaromatics: Combining catalysts for furan formation

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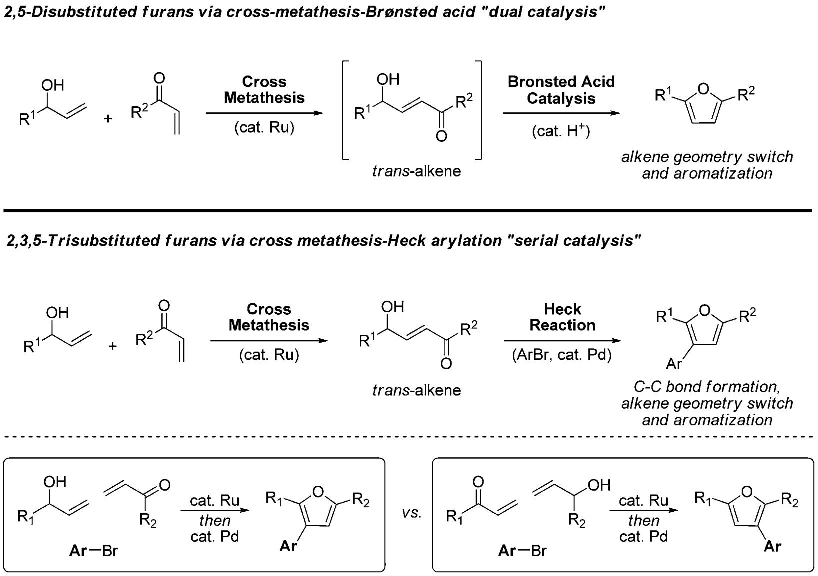
Ring-closing olefin metathesis (RCM) is an effective method for the formation of cyclic alkenes (1). Recently, the aromatization of RCM products has emerged as a topic of intensive investigation (2). In this context, a variety of regiocontrolled protocols have been developed for the synthesis of diverse heteroaromatic compounds, such as pyridines, pyridazines, pyrroles, quinolines, and furans (2). In all reported approaches, a key strategic consideration relates to the requirement of intermolecular fragment union in advance of the key RCM event. Strategies based on the use of intermolecular alkene metathesis, termed cross-metathesis, would potentially streamline access to aromatic structures by uniting the key steps of fragment coupling and alkene formation. However, the use of cross-metathesis in the synthesis of aromatic heterocycles is prohibited by the fact that *trans*-alkene products predominate (3, 4), which are unsuitable for cycloaromatization. A report by Donohoe and Bower (3) in this issue of PNAS resolves this problem, thus enabling rapid entry to substituted furans from readily available reactants.

To harness the power of cross-metathesis for arene construction, Donohoe and Bower (3) define tandem catalytic processes, wherein the initially formed products of cross-metathesis, the *trans*-alkenes, are converted to the corresponding *cis*-alkenes and, ultimately, the desired aromatic products. To accomplish this, these investigators take advantage of remarkable tolerance of the ruthenium-based metathesis catalysts to Brønsted acid cocatalysts. Cross-metathesis of allylic alcohols and unsaturated ketones (5, 6) was performed in the presence of substoichiometric quantities of Brønsted acid. It was found that the initially formed *trans*-alkene is subject to acid-catalyzed isomerization to furnish the transient *cis*-alkene, which undergoes acid-catalyzed condensation to deliver disubstituted furans (7) (Fig. 1, *Upper*). This combination of transition metal and Brønsted acid catalysis enables direct conversion of abundant acyclic reactants to furans in the absence of protecting groups and the preactivation associated with the construction of RCM substrates, as previously practiced.


2,5-Disubstituted furans via cross-metathesis-Brønsted acid "dual catalysis"

2,3,5-Trisubstituted furans via cross metathesis-Heck arylation "serial catalysis"

Fig. 1. (*Upper*) Union of transition metal and Brønsted acid catalysis enables direct conversion of enones and allylic alcohols to disubstituted furans. (*Lower*) Serial cross-metathesis-Heck arylation enables formation of trisubstituted furans. Regiospecific introduction of groups onto the furan core is achieved by programming the oxidation level of the cross-metathesis precursors.

In principle, the preparation of more highly substituted furans should require the cross-metathesis of more highly substituted allylic alcohols and enones. However, formation of requisiste trisubstituted enones via cross-metathesis is a demanding process, and one that is beyond the capability of the ruthenium catalysts presently available. Hence, to access trisubstituted furans, Donohoe and Bower (3) turn to the Heck reaction. Here, in two discrete steps, *trans*-configured enones formed by cross-metathesis are subjected to Heck arylation (8), which (*i*) selectively introduces a third substituent to the enone β-position and (*ii*) inverts the geometry of the initially formed *trans*-alkene such that arene formation can ensue in the same reaction vessel (Fig. 1, *Lower*). Notably, in this "serial" cross-metathesis-Heck reaction sequence, the oxidation level of the enone-allyl alcohol pair dictates the position of the third substituent. If the oxidation level of the enone-allyl alcohol pair is exchanged, so, too, is the placement of the third substituent (Fig. 1, *Lower*).

Further extension of this chemistry provides access to more complex furan derivatives. For example, substrates modified for intramolecular Heck reaction enable formation of an additional ring, representing a remarkably concise approach to complex fused polyaromatic ring systems. Additionally, cross-metathesis-based furan formation easily lends itself to the construction of furans embedded within macrocycles. Such motifs appear as key substructures in the furanocembranolide family of natural products (9, 10) (Fig. 2).

In summary, olefin metathesis, Brønsted acid catalysis, and the Heck reaction are powerful methods in their own right. As described in the paper by Donohoe and Bower (3), use of these catalytic processes in tandem allows one to construct functionalized furans from simple building blocks, representing a unique counterpoint to established methods for the derivatization of arenes by cross-coupling or C-H functionalization. Most significantly, one can easily envision application of related tandem cross-metathesis

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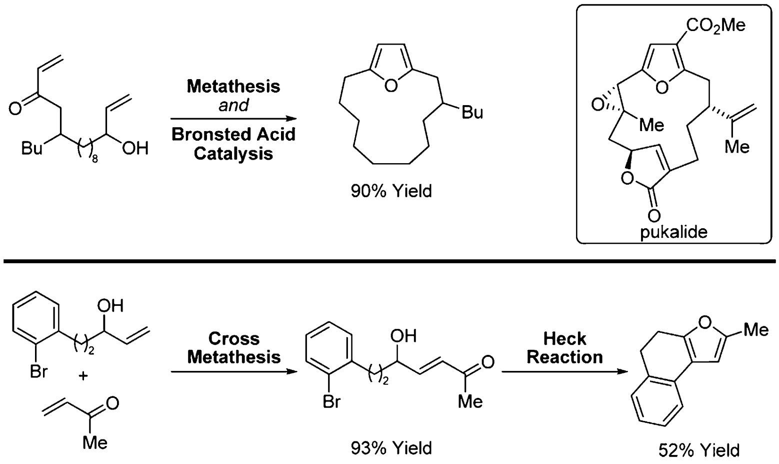

Fig. 2. (*Upper*) Furans embedded within macrocycles via "intramolecular cross-metathesis." (*Lower*) Polycyclic furans via intramolecular Heck arylation.

methodologies to the construction of other aromatic and heteroaromatic frameworks. Given the importance of substituted heteroaromatics to the pharmaceutical sector, the strategic concepts presented by Donohoe and Bower (3) will likely open a broad new avenue of investigation in the area of heteroaromatic chemistry.

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