

Synthetic Methods

Combinatorial Catalysis Employing a Visible Enzymatic Beacon in Real Time: Synthetically Versatile (Pseudo)Halometalation/Carbocyclizations**

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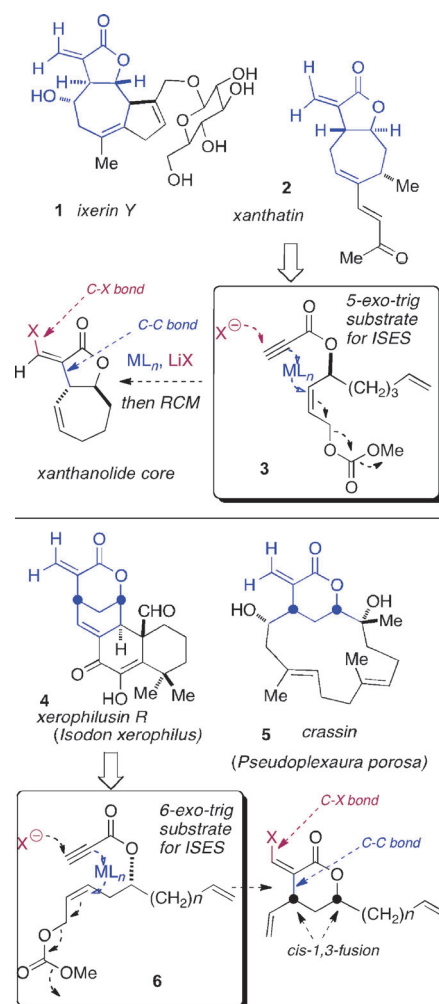
Combinatorial approaches to catalysis have made an impact in targeted transformation development, including silver-mediated carbene insertion,^[1] scandium/pybox-based (pybox = bis(oxazolonyl)pyridine) asymmetric cyclopropanation,^[2] and rhodium/iridium-based asymmetric hydrogenation.^[3] Useful design elements have emerged from these studies, for example, the value of ligand self-assembly,^[4] or of the inclusion of peptide-like structural elements^[5–7] in building ligand arrays. Efficient screening methods are of paramount importance for such efforts. Methods based on fluorescence,^[8] REMPI,^[9] MS,^[10] NMR,^[11] and IR thermography^[12] have appeared. A chromophore may be installed into the substrate^[13] or product^[14] of the reaction under study. Alternatively, one can exploit chromophores inherent in proteins^[15] or enzyme-associated reactions,^[16] and use these sensors to report back on product formation and composition.

Our group has developed an in situ enzymatic screening (ISES) approach whereby an organometallic reaction under study is coupled to an enzymatic reporting reaction in real time.^[17] This screening method led to the discovery of the first asymmetric allylic amination with nickel(0)^[18] and to the identification of novel salen [salen = *N,N'*-bis(salicylidene)-ethylenediamine)] ligands with promise for asymmetric synthesis.^[19] Those approaches involved dehydrogenase enzymes^[20] as sensors, thus utilizing the inherent nicotinamide cofactor to provide a UV signal.

Herein we describe an important new ISES mode in which the reporting enzymes lead to a visible signal in real time. The advantages of colorimetric approaches have been articulated^[13,21] and include the ability to screen a diverse array of catalysts with the naked eye, without employing specialized equipment, as well as increasing convenience and throughput.

Synthetically, this study was directed at developing formal halometalation/carbocyclization transformations. One can

envision this providing a rapid entry into the cores of terpenoid natural products featuring exomethylene γ -lactones (Scheme 1). The 6-*exo-trig* substrate **6** would lead into cores of xerophilusin and crassin, a specific modulator of STAT phosphorylation.^[22] The 5-*exo-trig* substrate **3** is designed to give 5,7-sesquiterpenoid lactone cores.^[23] Key natural products (NPs) here include the guaianolide, ixerin Y (**1**),^[24] and xanthatin (**2**), which shows anti-MRSA (methicillin-resistant *Staphylococcus aureus*),^[25] antifungal,^[26] and antiulcer^[27] activity.



Scheme 1. Proposed halometalation/carbocyclization routes leading to the core structures of terpenoid exomethylene lactone natural products.

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Related NP-derived α -methylene butyrolactone moieties appear to undergo Michael addition with Cys-38^[28] of the transcription factor NF- κ B,^[29] thereby blocking DNA binding.^[30] Our synthetic approach is particularly attractive in light of such structure–activity relationships (SAR), as it would deliver the NP core with a β -halo α,β -unsaturated lactone moiety, for potential target capture, in vivo, and also to tap into cross-coupling chemistry ex vivo for chain extension/library elaboration. The drive toward streamlined methods for the construction of such NP cores is motivated by the effectiveness of NP-core-based chemical biology libraries in defining studies by groups such as Schreiber,^[31] Waldmann,^[32] Shair,^[33] Arndt,^[34] and Snapper.^[35]

While the chemistry envisioned in Scheme 1 remained largely unexplored, there was some precedent from the work of Lu and co-workers,^[36a,b,c] who reported primarily on acetoxy metalation/carbocyclization employing Pd^{II} catalysis in neat acetic acid^[37] as solvent. We set out to examine a much broader spectrum of metal, (pseudo)halide, and substrate space combinatorially by using visual colorimetric ISES for higher throughput.

We demonstrate herein that the combination of alcohol oxidase and peroxidase serves as an effective reporting duo for the title transformation (Figures 1a and 1b). By utilizing 2,2-azino-bis(3-ethylbenzothiazoline-6-sulfonate) (ABTS), as a peroxidase cofactor, one achieves particular sensitivity. This sensitivity arises because each molecule of alcohol (by)product emanating from the organic reaction of interest that is oxidized by the alcohol oxidase reporter gives rise to two equivalents of the ABTS radical cation, thus providing an intense ($\epsilon_{405-414}$ (2 ABTS^{•+}) ca. 70000 M⁻¹ cm⁻¹)^[38] colorimetric signal in the visible range (jungle green). This allows first-pass scanning of a large number of potential catalytic combinations with the naked eye (Figure 2). A more quantitative ranking (relative rates) may then be obtained by UV/visible spectrophotometry on the first-pass hits (Figure 3).

A broad array of 64 metal catalyst candidates was chosen and subdivided into four groups of 16 catalysts each, as detailed in the Supporting Information. These were screened against six (pseudo)halides (LiF, LiCl, LiBr, LiCN, LiOCN, LiSCN) and three candidate substrates (**3**, **7**, and **8**), thereby creating a 64 $\times$ 6 $\times$ 3 = 1152 combinatorial array (see Figure 1c). Figure 2 shows a 96 well tray for the metal set III versus substrate **3**. These were run in a convenient 300 μ L format (200 μ L organic/100 μ L aq. enzymatic layer). One sees clear positive readouts for the combination of LiBr with both Rh^{II} perfluorocarboxylates (in contrast to the Rh^{II} carboxylate catalyst), as well as with [Pd^{II}(acac)] (but not [Ni^{II}(acac)]) and [PdCl₂(PhCN)₂] (but not [PtCl₂(PhCN)₂]).

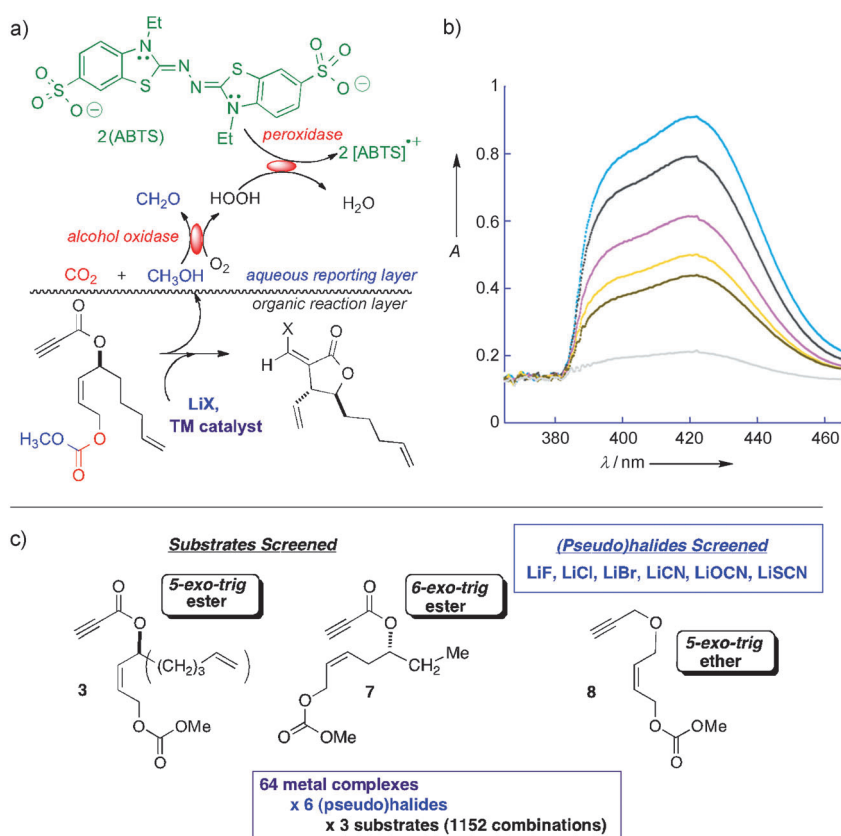


Figure 1. a) Schematic of the in situ screen; b) UV spectrum for the formation of the ABTS radical cation over time; c) the potential catalytic combinations screened.

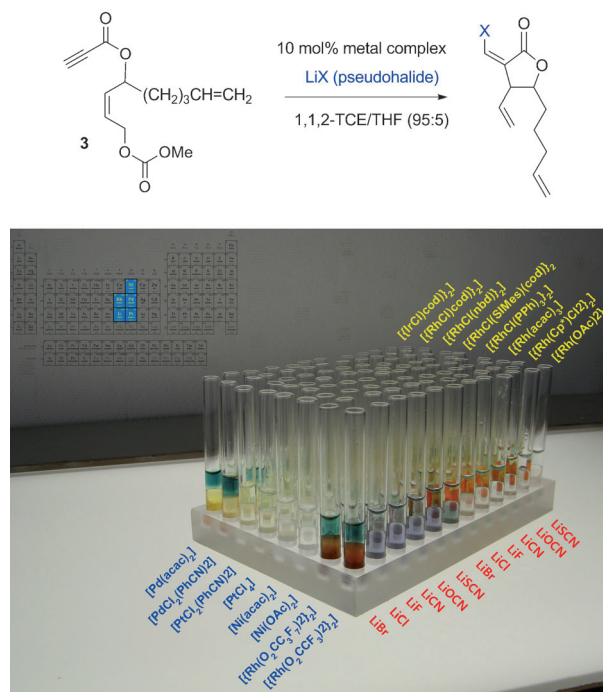


Figure 2. Example of a d9-d10 array for substrate **3**. 16 Metal complexes were screened across six (pseudo)halides with the propiolate ester **3** (5-exo-trig substrate). acac = acetylacetonate.

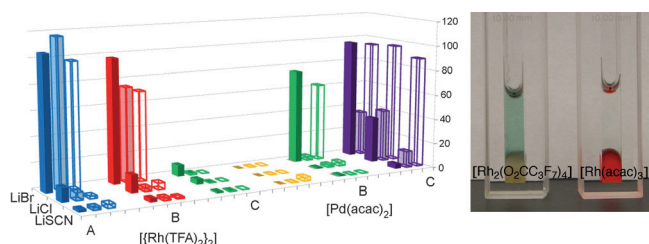


Figure 3. a) Initial hits from visual colorimetric ISES are ranked spectrophotometrically (Abs_{405} in $mAbs\ min^{-1}$; A, B, and C are substrates **3**, **7**, and **8**, respectively; see the Supporting Information for experimental details). b) An example of the cuvette ISES experiment. The ABTS indicator shows turnover with Rh^{II} perfluorobutyrate, whereas the highly colored Rh^{III} catalyst fails.

The most interesting hits in the colorimetric tray screen were then “cherry-picked” visually, and then ranked more quantitatively by spectrophotometric analysis in the cuvette (Figure 3). As can be seen, for Pd^{II} the cyclization chemistry proceeds efficiently with $[PdCl_2(PhCN)_2]$ and LiBr for both the 5-*exo-trig* ester and ether substrates. Acetic acid clearly is not necessary for these cyclizations. Among the other Pd^{II} catalysts screened, $[Pd(acac)_2]$, gave the next fastest rates.

However, the most generally effective catalytic combination found was LiBr with the Rh^{II} perfluorocarboxylates, which provided efficient formal bromorhodiation/carbocyclization across all three test substrates; this result was in stark contrast to the Rh^{II} acetate dimer, and all Rh^I and Rh^{III} complexes examined. This reactivity was verified under standard round bottom flask conditions, through which product identity, stereochemistry, and yield were established (Figure 4). Note that the cyclizations are highly diastereoselective, giving the 1,2-*trans* stereochemistry for the xanthatin core from **3**, and the 1,3-*cis* stereochemistry for the crassin-type core from **7**. Also of interest is that the catalyst loading

cyclization product	from 3	from 7	from 8	from 8	from 8
catalyst/nucleophile					
$[Rh(O_2CCF_3)_2]_2$ LiBr	80% ^[a] <i>trans/cis</i> 10:1	90% ^[a]	64% ^[a] <i>trans/cis</i> >20:1	66% ^[b] (37%)	—
$[Rh(O_2CCF_3)_2]_2$ LiBr	85% ^[a] <i>trans/cis</i> 11:1	90% ^[a]	58% ^[a] <i>trans/cis</i> >20:1	62% ^[b] (42%)	—
$[Pd(acac)_2]$ LiBr or LiSCN	80–89% <i>trans/cis</i> ~19:1	94%	< 15% ^[a]	73% ^[b]	—
$[PdCl_2(PhCN)_2]$ LiBr or LiSCN	88–92% <i>trans/cis</i> ~20:1	95%	30% ^[a]	85% ^[b] (48%)	89%

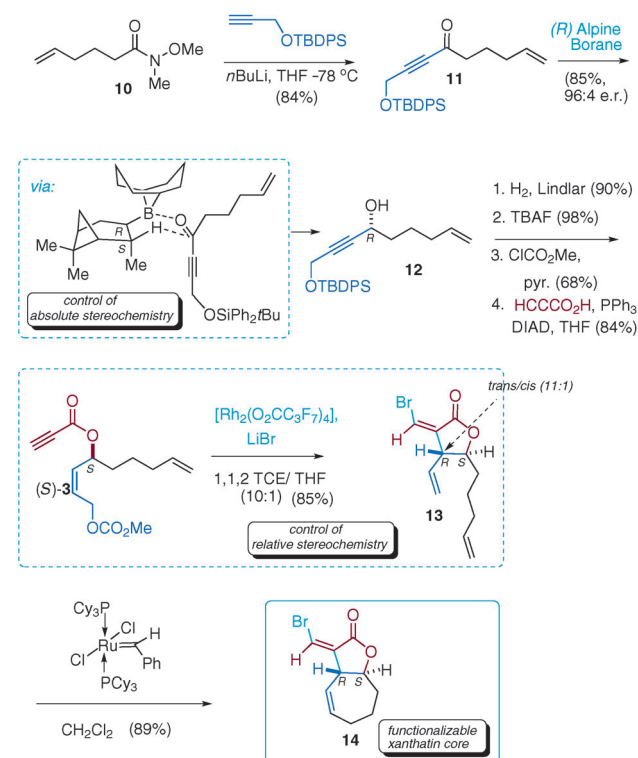
Figure 4. Chart showing the success of catalytic metal/(pseudo)halide combinations as a function of substrate. Yields of the isolated products for the homogeneous material after running the reactions under standard round bottom flask conditions and purifying the resulting products by chromatography on silica gel. [a] Reaction carried out at 60 °C. [b] Yield determined by GC methods.

could be lowered to 2.5 mol% by using gentle heating or sonication without compromising the yield (see the Supporting Information).

This reaction would appear to constitute a new reaction mode for the Rh^{II}/LiX combination. Control experiments established that this reactivity is not a function of stray trifluoroacetic acid (see the Supporting Information). The disparate reactivity of Rh^{II} perfluorocarboxylates versus Rh^{II} carboxylates is reminiscent of the observations reported by Padwa, Doyle, et al., that is, the tendency of only the Rh^{II} perfluorocarboxylate to promote electrophilic aromatic substitution over carbene insertion.^[39] Clearly this unusual and valuable reactivity warrants further exploration.

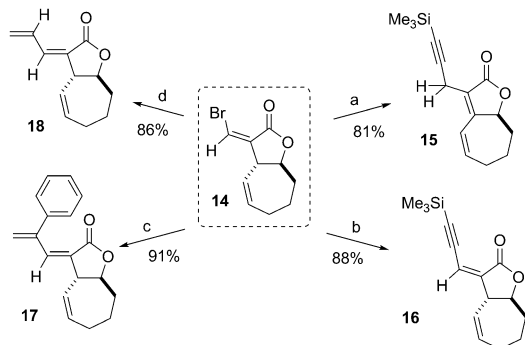
Perhaps of equal significance is the combination of $[PdCl_2(PhCN)_2]$ with LiSCN, which yields an unprecedented formal thiocyno palladation/carbocyclization transformation. As such, this reaction assembles a cyclic NP-core bearing a terminal vinyl thiocyanate in one operation (the product structure was verified both spectroscopically and chemically; see the Supporting Information). Given the importance of the thiocyanate functionality for elegant vibrational Stark-effect studies to probe active-site environments carried out by Boxer and co-workers,^[40] this transformation will likely be of real value to chemical biologists.

We next utilized the new Rh^{II} perfluorocarboxylate chemistry to fashion a library of small compounds based on the xanthatin core, which was obtained through stereocontrolled synthesis and then tailoring chemistry (Scheme 2).



Scheme 2. Application of the new halometalation/carbocyclization route to the stereocontrolled synthesis of the xanthatin core. DIAD = diisopropylazodicarboxylate, pyr = pyridine, TBAF = tetra-*n*-butylammonium fluoride, TBDPS = *tert*-butyldiphenylsilyl, 1,1,2-TCE = 1,1,2-trichloroethane, THF = tetrahydrofuran.

Alpine borane mediated ynone reduction establishes the absolute stereochemistry^[41] (see the Supporting Information) and the bromometallation/carbocyclization sets the relative stereochemistry. Finally, ring-closing metathesis yields the desired xanthanolide core with the bromomethylene lactone functionality **14**, which undergoes palladium-mediated chain extension reactions as shown in Scheme 3.



Scheme 3. Exploitation of the bromomethylene lactone functionality for transition metal mediated tailoring chemistry upon the bicyclic xanthanolide core: a) $\text{HC}\equiv\text{C}-\text{SiMe}_3$, CuI, $[\text{PdCl}_2(\text{PPh}_3)_2]$, Et_3NH ; b) $\text{Bu}_3\text{SnC}\equiv\text{C}-\text{SiMe}_3$, cat. $[\text{Pd}_2(\text{dba})_3]$, Pfur, Δ ; c) $\text{BrZnC}(\text{Ph})\text{C}=\text{CH}_2$, $[\text{Pd}(\text{PPh}_3)_4]$, Δ ; d) $\text{Bu}_3\text{SnCH}=\text{CH}_2$, $[\text{Pd}_2(\text{dba})_3]$, Pfur, Δ . dba = dibenzylideneacetone, fur = furyl.

Note that the standard Sonogashira coupling proceeds with double-bond migration, thus yielding the bicyclic dienolate in **15**. Use of modified Stille coupling conditions (i.e., stannylated acetylene) prevents this migration and gives ynenolate **16** instead. All analogues feature more extended Michael acceptors that are of potential interest, given the mechanistic hypothesis that has been advanced (see above). In summary, the first application of visible, colorimetric ISES has uncovered both a generalizable Rh^{II} perfluorocarboxylate/ LiBr -mediated halometallation/carbocyclization and the first formal thiocyanometallation/carbocyclization. Current efforts are focused on exploring the scope of these new tandem bond constructions, and the colorimetric screen that led to their discovery.

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