Titanocene-Catalyzed Multicomponent Coupling Approach to Diarylethynyl Methanes

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Supporting Information

ABSTRACT: A titanocene-catalyzed multicomponent coupling to provide diarylethynyl methanes is described. By combining the multifunctionality of Cp2TiCl2 with the traceless dielectrophilicity of aryl aldehydes, all-carbon tertiary centers are obtained in 55−99% yield.

The addition of carbon nucleophiles to carbonyl derivatives remains one of the foremost strategies to construct C−C bonds.1 However, the synthesis of highly substituted all-carbon centers from a carbonyl precursor typically requires multiple synthetic operations, including a deoxygenation step that often leads to issues of chemoselectivity.2 To address these obstacles that limit the utility of this ubiquitous functional group, we sought a protocol that enables the addition of two distinct carbon nucleophiles employing a single transition metal catalyst in a synthetically efficient manner (eq 1). Based on our previous work toward 1,4-diynes,3 we speculated that employing aryl nucleophiles in a titanocene-catalyzed multicomponent coupling would enable the direct assembly of unsymmetrical diarylethynyl methanes (eq 2).

The diaryl-substituted tertiary carbon is a prevalent structural motif in nature, as exemplified by ampelopsin D (1),5 fischerisin A (2),6 and calyxins B (3) and C (4) (Figure 1). The intriguing biological properties associated with these natural products make this architectural subunit a worthy synthetic target.8 A one-pot diarylethynyl methane synthesis directly from aldehydes offers the opportunity for a flexible and modular synthesis of this substructure. Additionally, incorporation of the alkyne unit provides a versatile functional handle for further secondary transformations. Herein, we report a highly convergent assembly of tertiary all-carbon centers that exploits the redox and Lewis acidic properties

Received: September 6, 2012
Published: October 21, 2012

Figure 1. Diarylmethane-containing natural products.
Furthermore, exposing diarylethane 5c to identical conditions provided the seven-membered ring adduct 7c in 77% yield.

Emboldened by our initial success in constructing cyclic diarylethynyl methanes, we turned our attention toward examining the feasibility of an intermolecular multicomponent coupling. Gratifyingly, subjection of aldehyde 9a, arene 10a, and iodoalkyne 6a to our titanocene-catalyzed coupling conditions gave diarylethynyl methane 11a in 77% yield (eq 5). Extending this initial finding to heteroaryl nucleophiles led to the successful coupling with N-methylindole (10b), aldehyde 9b, and 6a to provide diarylethynyl methane 11b, resulting from exclusive indole C3 alkylation, in 68% yield (eq 6). Given the pharmaceutical significance of indole alkaloids,10 and the synthetic versatility of alkynes, this method constitutes a powerful tool for the synthesis of functionalized indoles.11

Upon examination, we discovered that the titanocene-catalyzed multicomponent coupling of aryl aldehydes 9 and arenes 10 with 6a proved general for a wide array of functionally diverse substrates (Table 1). Alkylation of electron-rich and electron-poor aldehydes 9c and 9d with indole 10b provided the expected diarylethynyl methanes in good yields (entries 1 and 2). Additionally, the presence of an N-acyl protecting group on indole 10c did not adversely affect the formation of 11e (entry 1). The coupling of aldehydes bearing an indole (9e), furyl (9f), or thiophenyl (9g) heteroaryl ring with indole 10b and 6a yielded the unsymmetrical diarylethynyl methanes 11f–h respectively in 68–71% yields (entries 3–5). Consistent with our initial findings, electron-rich aryl rings proved superior to their neutral and electron-deficient counterparts. The addition of C2-substituted indole 10d and 6a to aldehyde 9c provided adduct 11i in 80% yield (entry 6). Coupling of aldehyde 9c and 6a with either furan 10e or aniline 10f provided adducts 11j and 11k in excellent yields (entries 7 and 8). Finally, aniline 10f also proved effective in the coupling of 3-formylindole 9e and 6a to yield 11l (entry 9).

The titanocene-catalyzed coupling also proved general for a range of iodoalkynes 6 in the alkylation of aldehyde 9c and indole 10b (Table 2). Electron-rich and electron-poor aryl iodoalkynes 6b–d provided the corresponding diarylethynyl methanes 11m–o in good yields (entries 1–3). Aliphatic alkynyl iodides 6e and 6f gave propargyl indoles 11p and 11q in 80% and 58% yield, respectively (entries 4 and 5). Silyl iodoalkyne 6g, an effective acetylene surrogate, coupled efficiently with 9c and 10b to yield diarylethynyl methane 11r (entry 6). It is noteworthy that, although both iodoalkyne and Ar–H nucleophiles are present throughout the reaction, the formation of 1,4-diynes or triaryl-methanes was not observed.

In an effort to evaluate a more structurally complex component, we chose iodoalkyne 6h, corresponding to the C1–C6 fragment of the acyclic calyxin diaryleptanoids illustrated in Figure 1 (eq 7). Construction of enantioenriched 6h was
accomplished in three steps from known aldehyde 12 using a
titanium-catalyzed asymmetric propargylation.13 Treatment of
6h, aldehyde 9h, and arene 10g with Cp2TiCl2 (5 mol%),
'tBu3P, Zn, Cs2CO3, and Ac2O provided diarylethynyl methane
11s in 99% overall yield as a 1:1 mixture of C7 epimers (eq 8).
Interestingly, 40 mol% of P'tBu3 was required for full conversion,
whereas 80 mol% led to arrest at the intermediate propargylic
acetate. Notably, unreacted arene and the terminal alkyne, resulting
from reduction of iodoalkyne 6h, were recovered quantitatively.

Consistent with our previous work involving the titanocene-catalyzed metalation of C−X bonds,3,9d,14 there appears to be
a synergistic effect of Cp2TiCl2, Zn0, and 'Bu3P in formation
of the first C−C bond resulting from acetylide addition to
aldehyde 9.9c,15 This is supported by the observation that, in
the absence of Cp2TiCl2, Zn0, or Ac2O after prolonged reaction
times (>48 h), only starting aldehyde or propargylic alcohol/
acetate was obtained. In contrast to the redox assembly of 1,4-
diyynes,9 the second C−C bond-forming event en route to
diarylethynyl methanes likely occurs via a Lewis acid-catalyzed
propargylic arylation involving either an oxophilic titanocene
complex or Zn11 salt.16 However, a single electron transfer redox
process involving an SnAr1 aromatic substitution catalyzed by
Cp2TiCl cannot be excluded at this time.9c Additional evidence
for a propargylic cation or radical intermediate was obtained by
treating cinnamaldehyde with indole 10b and iodoalkyne 6a
under the reaction conditions to yield a 1:1 mixture of allylically
transposed arylation products. Although the role of phosphine
is unclear at this stage, it may serve to stabilize low-valent titanocene
intermediates, while increasing the reactivity of metal acetylides
through an unusual P–Zn ligation.17

In summary, we have developed a versatile approach toward
diarylethynyl methanes by harnessing the multifunctional attri-
butes of low valent titanocene. This multicomponent coupling
permits a high degree of modularity and convergency in the rapid
assembly of complex targets around the construction of a single
all-carbon substituted tertiary center. The application of this
method to the synthesis of biologically active natural products,
and studies aimed at elucidating the mechanism of C−C bond
formation, are currently underway and will be reported in due
course.

ASSOCIATED CONTENT

Supporting Information
Experimental procedures and characterization data. This
material is available free of charge via the Internet at http://
pubs.acs.org.

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Notes
The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the University of Notre Dame for financial support of
this research.

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Table 2. Iodoalkyne Componenta

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product, %</th>
<th>Yield, %</th>
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<tr>
<td>1</td>
<td>MeO 6b</td>
<td></td>
<td>83%</td>
</tr>
<tr>
<td>2</td>
<td>Cl 6c</td>
<td></td>
<td>83%</td>
</tr>
<tr>
<td>3</td>
<td>F3C 6d</td>
<td></td>
<td>80%</td>
</tr>
<tr>
<td>4</td>
<td>'Bu 6e</td>
<td></td>
<td>80%</td>
</tr>
<tr>
<td>5</td>
<td>BnOCH2 6f</td>
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<td>58%</td>
</tr>
<tr>
<td>6</td>
<td>TIPS 6g</td>
<td></td>
<td>67%</td>
</tr>
</tbody>
</table>

Conditions: same as Table 1. Isolated yields.
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