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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

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Application of In Situ-Generated Rh-Bound Trimethylenemethane Variants to the Synthesis of 3,4-Fused Pyrroles

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Supporting Information

ABSTRACT: Rh-bound trimethylenemethane variants generated from the interaction of a Rh-carbenoid with an allene have been applied to the synthesis of substituted 3,4-fused pyrroles. The pyrrole products are useful starting points for the syntheses of various dipyrromethene ligands. Furthermore, the methodology has been applied to a synthesis of the natural product cycloprodigiosin, which demonstrates antitumor and immunosuppressor activity.

The trimethylenemethane (TMM) moiety (Figure 1) has a rich history in bonding and reactivity that dates back to

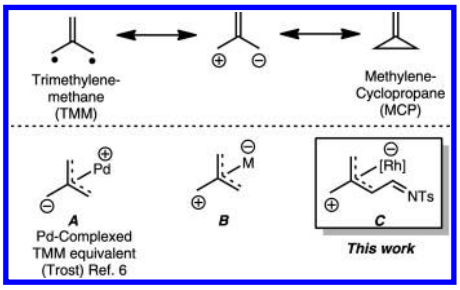
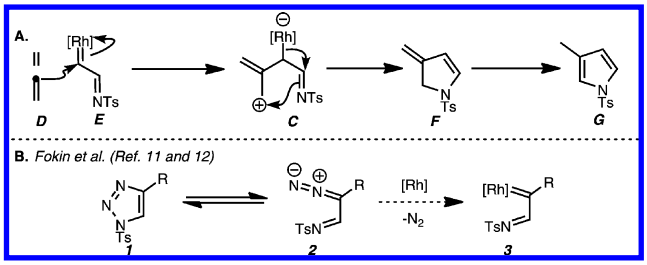


Figure 1. Trimethylenemethane equivalents.

the seminal work of Moffitt[1] and pioneering studies of Dowd.[2,3] The connection between TMM and methylenecyclopropane (MCP) is well-recognized, and many studies have shown that the parent TMM is a ground-state triplet with a low barrier for conversion to the singlet and thus closes almost instantaneously to the corresponding MCP.[3b] To exploit the reactivity of TMMs in synthetic applications, they are often constrained as a part of a ring[4] or complexed to a metal center. As a result, many metal-mediated processes that convert MCPs to metal-complexed TMMs have been reported over the last two decades.[5] By far the most recognized and utilized metal-complexed TMM is **A** (Figure 1), where the Pd is intimately associated with the cationic termini. The Pd−TMM complex **A** was introduced by Trost[6] and has been featured as a "three-carbon partner" in numerous cycloaddition reactions. Despite the now well-established utility of metal-complexed TMM variants, there have been comparatively few reported TMM equivalents where the metal is bound to the anionic portion of this reactive intermediate (see **B**). In this communication, we report the generation of unique Rh-bound TMM derivatives **C** that are related to **B** and can be applied in the synthesis of 3,4-fused pyrrole derivatives. Contemporaneous with our studies, Davies and coworkers have developed an elegant related methodology for the synthesis of substituted pyrroles that utilizes furan starting materials.[7] The 3,4-fused pyrrole structures that we have prepared feature prominently in several ligand motifs, especially of the dipyrromethene type. As further testament to the utility of this methodology, we have applied it to the total synthesis of the natural product cycloprodigiosin.

We envisioned Rh-complexed TMM equivalent **C** arising from the interaction between allene moiety **D** and imino Rh-carbenoid **E** (Scheme 1A).[8] The nitrogen atom of the *N*-

Scheme 1. Proposed Application of Rh−TMM to Pyrrole Formation



tosylimine group in **C** could then engage the allyl cation to provide dihydropyrrole derivative **F**, which could aromatize to pyrrole **G** following double bond migration.[9,10]

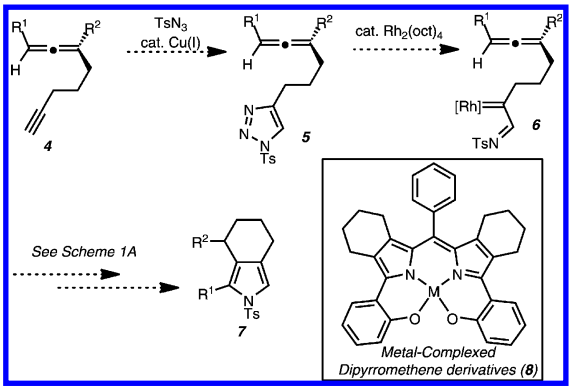
The success of the general transformation outlined in Scheme 1A hinges on the effective generation of Rh-carbenoids related to **E**, which have recently been demonstrated to arise from the decomposition of *N*-sulfonyl-1,2,3-triazoles by Fokin, Gevorgyan, and co-workers (Scheme 1B).[11,12] Specifically, we were drawn to an intramolecular variant of the transformation shown in Scheme 1A wherein allenylalkynes (**4** in Scheme 2) could be subjected to Cu-catalyzed Huisgen cycloaddition[13] to yield **5**. On the basis of the observations of Fokin and co-workers, it was anticipated that exposure of **5** to catalytic $Rh_2(oct)_4$ would lead to the formation of *N*-sulfonylimino Rh-carbenoid intermediate **6**, which following the sequence outlined in Scheme 1A would yield fused *N*-tosylpyrrole **7**. Pyrrole derivatives related to **7** are highly valuable starting points for the preparation of dipyrromethene ligands, which have various applications including use as dyes[14] and scavengers of reactive oxygen species (e.g., as in **8**).[15]

One significant potential pitfall of our planned transformation of **4** to **7** was the possibility that Rh-carbenoid

Received: February 6, 2013
Published: March 11, 2013

   dx.doi.org/10.1021/ja401380d | *J. Am. Chem. Soc.* 2013, 135, 4696−4699

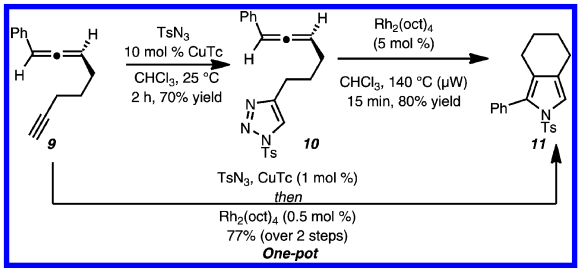
Scheme 2. Intramolecular Pyrrole Annulation Reaction for the Formation of 3,4-Fused Pyrroles



intermediates related to **6**, consistent with well-documented precedent,[16] would undergo a competing 1,2-hydride shift to yield α,β-unsaturated *N*-tosylimines instead of engaging the allene group. Although 1,2-hydride shifts of α-keto Rh-carbenoids have been shown to be minimal at lower temperature,[17] Murakami showed that this pathway is facile for α-*N*-sulfonylimino Rh-carbenoids,[18] especially at the high temperatures that are required for the decomposition of *N*-tosyl-1,2,3-triazoles to the corresponding Rh-carbenoids (>100 °C). As a result, the successful transformation of **4** to **7** would require that the 1,2-hydride shift from the Rh-carbenoid intermediates did not compete with the desired pathway.

We initiated our studies with allenylalkyne **9** (Scheme 3), which was readily prepared in three steps from phenylacetylene

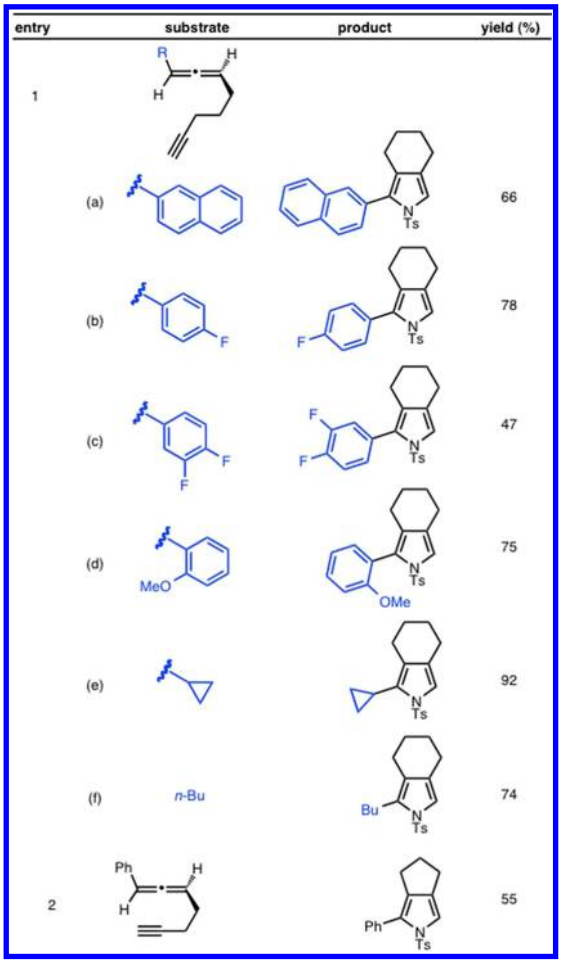
Scheme 3. Development of One-Pot Conditions for Pyrrole Formation



and trimethylsilyl (TMS)-protected hex-5-ynal.[19] The copper(I) thiophene-2-carboxylate (CuTc)-catalyzed Huisgen cycloaddition of **9** with TsN_3 proceeds without event to give *N*-tosyl-1,2,3-triazole **10** in 70% yield following column chromatographic purification. Gratifyingly, exposure of **10** to $Rh_2(oct)_4$ (5 mol %) in $CHCl_3$ at 140 °C (microwave), following the conditions of Fokin and Murakami,[20] gives 2,3,4-substituted pyrrole **11** in 80% yield. Since both the Cu-catalyzed Huisgen azide−alkyne cycloaddition and the Rh-catalyzed triazole decomposition/pyrrole formation were conducted in chloroform, the development of a one-pot sequence to convert **9** to **11** was straightforward. Importantly, the catalyst loadings of both CuTc and $Rh_2(oct)_4$ could be reduced significantly (to 1 and 0.5 mol %, respectively), and **11** is obtained in higher overall yield (77% yield over two steps) than in the sequence where the triazole intermediate was isolated and purified.[21]

Under the optimized one-pot conditions, a range of allenylalkyne substrates are efficiently transformed to the corresponding fused pyrroles (Table 1). For example, a variety

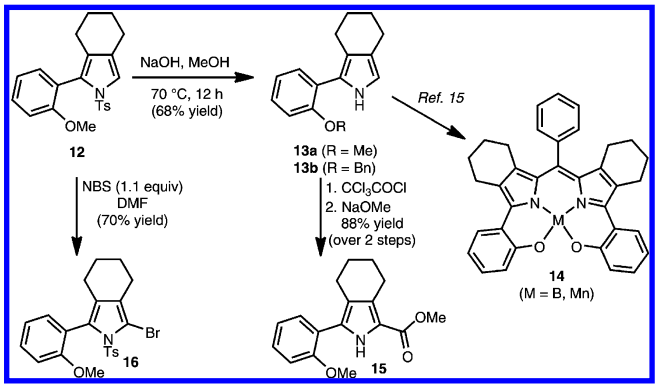
Table 1. Scope of 3,4-Fused Pyrrole Formation



of aryl substituents, including a naphthyl group (entry 1a) as well as arenes bearing electron-withdrawing (entries 1b and c) and electron-donating (entry 1d) groups on the allenylalkyne substrates are tolerated. In addition, cycloalkyl- and alkyl-bearing substrates are transformed to the corresponding pyrrole products in good yields (entries 1e and 1f). A bicyclo[3.3.0]-pyrrole, which is inherently more strained than the corresponding bicyclo[4.3.0] systems,[22] could also be accessed (entry 2), albeit in a slightly diminished overall yield (55%).

The utility of the 3,4-fused pyrrole products is evident in the conversions involving **12** (Scheme 4). For example, the related benzyl derivative **13b** was readily transformed to dipyrrome-

Scheme 4. Further Functionalization of 3,4-Fused Pyrroles

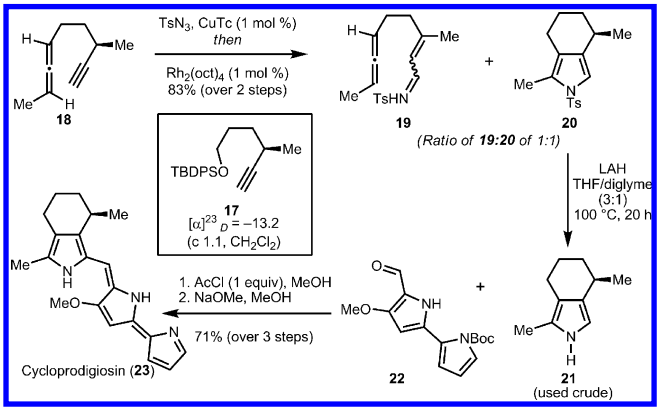


dx.doi.org/10.1021/ja401380d | J. Am. Chem. Soc. 2013, 135, 4696−4699

thene derivative **14**, a peroxynitrite scavenger, by Neumann and co-workers.[15] Furthermore, **13a** and **12** can be transformed to ester-substituted pyrrole **15** and bromo derivative **16**, respectively, in good yields in preparation for subsequent pyrrole functionalization reactions.

In addition to the applications detailed in Scheme 4, we applied our method for 3,4-fused pyrrole synthesis to the total synthesis of the natural product cycloprodigiosin (**23**) (Scheme 5[23]). Although this natural product, which is produced by

Scheme 5. Synthesis of Cycloprodigiosin (23)



bacterial strains including *Pseudoalteromonas (Alteromonas) rubra*, *Pseudoalteromonas denitrificans*, and *Vibrio gazogenes*, has been known for a long time,[24] its true structure was only secured in 1983.[25] Since that time, it has emerged as a potent proapoptotic anticancer compound[26] and immunosuppressant.[27] Over the past two decades, there has been sustained synthetic interest in the prodigiosin family as a whole.[28] However, the only synthesis of cycloprodigiosin, which was reported by Wasserman, appeared in 1984.[29] Our synthesis of **23** began with enantioenriched allenylalkyne **18**, which was prepared in six steps from known alkyne **17** as a mixture of diastereomers.[30] Under the conditions for pyrrole annulation outlined in Scheme 3, **18** was transformed in 83% yield to a 1:1 mixture of α,β-unsaturated imine **19** and the desired pyrrole **20**.[31] Presumably, the higher propensity of the methine hydrogen atom in **18** toward migration (compared with the methylene hydrogens as described for the substrates in Table 1) results in the competing formation of a significant amount of **19**. Efforts to minimize the formation of **19** using other metal salts or complexes known to modulate the reactivity of carbenes,[32] including $Rh_2(TFA)_4$, $Rh_2(cap)_4$, $Rh(OAc)_2(PC)_2$ (PC = ortho-metalated phosphine),[33] $RuCl_2(PPh_3)_3$, AgOBz, and Cu(*tert*-butylsalicylimine)$_2$,[34] resulted either in low conversion [with Cu(*tert*-butylsalicylimine)$_2$ and $Rh_2(cap)_4$], the exclusive formation of **19** [with $Rh_2(TFA)_4$], or nonspecific decomposition. However, with access to reasonable quantities of **20**, we proceeded with the synthesis by attempting to remove the tosyl group to give pyrrole **21**. Among the many conditions for tosyl group removal that we surveyed,[35] only the use of lithium aluminum hydride (LAH) successfully accomplished the conversion of **20** to **21**,[36] which was carried on crude to the next step. Condensation of **21** with **22** using the conditions of Lindsley[37] afforded cycloprodigiosin (**23**) in 71% yield over the three steps from **20**. The ^{1}H and ^{13}C NMR spectral data for synthetic **23** were in close agreement with those reported by Laatsch and Thomson.[25b] Our synthesis of **23** is the first enantioselective synthesis of cycloprodigiosin and should enable a full evaluation of the influence of the methyl-bearing stereocenter on the biological properties of the natural product.[38]

In conclusion, we have reported the synthesis of 2-substituted 3,4-fused pyrroles from allenylalkyne substrates. The one-pot transformation has its basis in a hypothesis for accessing unique Rh-bound trimethylenemethane intermediates. The pyrrole products should prove to be versatile starting points for a range of applications, as illustrated by the conversion of **13b** to a dipyrromethene derivative as well as the conversion of **12** and **13a** to other multiply substituted pyrroles. We have also applied the 3,4-fused pyrrole synthesis methodology to the synthesis of the natural product cycloprodigiosin. Our current efforts are centered on exploring the utility of this reaction in the synthesis of natural-product-like structures and novel dipyrromethene ligands.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic 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 are grateful to Prof. Huw Davies (Emory University) for sharing with us unpublished results of his research group's study of pyrrole formation using triazoles and furans. Our work was supported by the NSF (CAREER 0643264 to R.S.) and a Research Scholar Grant from the American Cancer Society (RSG-09-017-01-CDD to R.S.). R.S. is a Camille Dreyfus Teacher Scholar. We are grateful to the NSF for a graduate fellowship to E.E.S. and to Abbott, Eli Lilly, and Roche for financial support.

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(22) (a) This may be extrapolated from the strain energies inherent in *cis*-bicyclo[3.3.0]octane (10.67 kcal/mol) vs *cis*-bicyclo[4.3.0]nonane (7.75 kcal/mol). See: Allinger, N. L. *Molecular Structure: Understanding Steric and Electronic Effects from Molecular Mechanics*; Wiley: Hoboken, NJ, 2010; Chapter 11. (b) In the cases where moderate yields of the pyrrole products were obtained (<75% yield over the two steps), small amounts of α,β-unsaturated imine byproducts were also detected.
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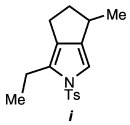
(31) The isomeric 3,4-fused pyrrole **i** was obtained in trace amounts as well.



i

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(38) (a) This is especially important since the reports on the isolation and subsequent work with cycloprodigiosin do not comment on whether it was obtained as a scalemic or racemic mixture. (b) Small amounts of an isomeric compound derived from **i** (see ref 31) were obtained along with **23** (see the SI).

NOTE ADDED AFTER ASAP PUBLICATION

The Table of Contents graphic and Scheme 5 were incorrect in the version published ASAP March 15, 2013. The corrected version was re-posted on March 19, 2013.