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C-H Bond Functionalization via Hydride Transfer: Direct Coupling of Unactivated Alkynes and sp³ C-H Bonds Catalyzed by Platinum Tetraiodide

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Abstract

We report a catalytic intramolecular coupling between terminal unactivated alkynes and sp^3 C-H bonds via the through-space hydride transfer (HT-cyclization of alkynes). This method enables one-step preparation of complex heterocyclic compounds by α-alkenylation of readily available cyclic ethers and amines. We show that PtI_4 is an effective Lewis acid catalyst for the activation of terminal alkynes for the hydride attack and subsequent C-C bond formation. In addition, we have shown that the activity of neutral platinum salts (PtX_n) can be modulated by the halide ligands. This modulation in turn allows for fine-tuning of the platinum center reactivity to match the reactivity and stability of selected substrates and products.

Introduction

C-H bond functionalization provides strategically new opportunities in the synthesis of complex organic compounds.[1] As part of a broad program aimed at the development of new approaches and methods for the direct functionalization of C-H bonds, we have been interested in the intramolecular coupling of sp^3 C-H bonds and alkenes to effect α-alkylation and α-alkenylation of ethers and amines under catalytic, non-basic conditions. To complement approaches initiated by transition metal insertion into a desired C-H bond,[2] we explored an alternative mode of reactivity based on Lewis acid catalyzed hydride transfer, followed by C-C bond formation (HT-cyclization). We have demonstrated that a wide range of substrates containing activated alkenes undergo cyclization under mild acidic conditions.[3,4] Subsequently, other laboratories demonstrated the feasibility of HT-cyclization with activated alkynes containing electron-withdrawing groups.5 We here report that unactivated terminal alkynes serve as hydride acceptors in *the through-space hydride transfer*, and undergo catalytic intramolecular hydroalkylation at the α-position of cyclic ethers and amines, providing rapid access to bicyclic products (Scheme 1).

The hydroalkylation of terminal alkynes has previously been limited to aromatic substrates, namely 2-alkyl-1-ethynylbenzenes, reported to give substituted indenes via an overall 5-*endo* cyclization (Scheme 2).[6,7,8,9] Different mechanistic rationales were proposed for this transformation including direct insertion of the metal-vinylidene group into the benzylic C-H bond in the intermediate II (formed *in situ* from the alkyne),[6] or a 1,5-sigmatropic hydrogen shift along the π-system.[7,8] More recently, the through-space 1,5-hydride transfer, followed

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Supporting Information Available. Experimental procedures and spectroscopic data for starting materials and products. This material is available free of charge via the Internet at http://pubs.acs.org.

by 6π-electrocyclization and reductive elimination, was proposed as a viable mechanism for the metal catalyzed cyclization of 2-alkyl-1-ethynylarenes.[8]

We here describe a distinct process, the 5-*exo* alkenylation of *saturated* heterocycles, which proceeds via the through-space hydride transfer, as the other mechanistic pathways (i.e., carbene insertion or sigmatropic rearrangement) are not plausible. We also report on the key importance of the platinum-halide bond in the modulation of the catalyst activity. The catalytic alkenylation of cyclic ethers and cyclic amines affords products of high synthetic value that are not readily accessible via other approaches.[10]

Results

Identification of the Catalytic System: Platinum versus Gold

Our approach is based on Lewis acid activation of the terminal alkyne and the subsequent hydride transfer (Scheme 1). We selected alkyne **1** as the first substrate; it is readily available in one step by propargylation of the corresponding malonate (Figure 1). As recent efforts point to the superiority of gold and platinum catalysts for the activation of alkynes,[11] we examined salts of these two metals in detail (see Supporting Information).[12] Surprisingly, substrate **1** gave only small amounts of the desired product **2** in the presence of a variety of gold catalysts, leading to complex mixtures of many products (e.g., $Ph_3PAuCl/AgOTf$ afforded <10% of product **2**). In contrast, platinum salts provided promising leads. For example, $PtCl_2$ (5 mol%, 120 °C, in MeCN) afforded the desired product **2** in 23% yield (Figure 1). Although the yield was low, the reaction mixture was clean, containing the product and the starting material (58% was recovered) as the two major species. Following this lead, we examined the effect of silver salt additives that usually lead to more electrophilic metal centers by generating cationic complexes *in situ*. In this case, however, no improvement was achieved; instead, lower yields of the desired product **2** were obtained in comparison to $PtCl_2$ itself (Table S1 in Supporting Info. provides a complete list of examined conditions).

Importance of the Platinum-halide Bond for the Catalyst Activity

At this point, we considered other possibilities for increasing the electrophilicity of the platinum catalyst, focusing our attention on the nature of the halide ligand and the platinum-halide bond. As a qualitative hypothesis, we considered the increasing size and the bond length, as well as the trend in the spectrochemical series, when moving from the chloride to the iodide ligand. We predicted that platinum iodides in comparison to other halides should be more electrophilic and the platinum metal more accessible to the alkyne, resulting in a more active catalyst.[13]

Guided by this qualitative rationale, the activity of platinum halide salts was systematically examined (Figure 1). We found that at 5 mol% loading, $PtBr_2$ afforded product **2** in 43% yield, while PtI_2 furnished **2** in even higher yield of 69% (Figure 1, the inset). In an attempt to further increase the efficiency of the reaction, we examined PtI_4 as we have previously shown the superiority of $PtCl_4$ to $PtCl_2$ in the hydroarylation of alkynes - with the rationale that the higher oxidation state renders a more electrophilic metal center.[14] Indeed, PtI_4 effected complete conversion of the starting material and provided the product in 86% yield.

In order to confirm that the halide effect was due to increased catalyst activity, and not to catalyst stability, we investigated the initial rates of product **2** formation under the action of different platinum catalysts (Figure 1, the plot). Fitting with the observed trend in yield, the rate of reaction was found to increase from the chloride to the iodide ligand: $PtBr_2$ afforded the faster initial rate than $PtCl_2$, while the platinum iodides exhibited far greater initial rates compared to $PtCl_2$ and $PtBr_2$. Although PtI_2 showed a marginally faster initial rate than PtI_4,

in terms of the yield, PtI_2 was consistently inferior. The PtI_2 catalyzed reactions failed to proceed to completion most likely due to the lower stability of this catalyst.

Thus, 5 mol% of PtI_4 afforded the desired product **2** in 86% yield with complete consumption of the starting material after 3 hours at 120 °C. With these optimized conditions in hand, we set out to examine the scope of this new reaction (Table 1).

Substrate Scope of the HT-cyclization

We first explored the cyclic amine substrates owing to their considerable synthetic importance. The methyl carbamate substrate **3** was synthesized to enable direct comparison to the corresponding ether **1**. As expected, the carbamate substrate, proceeding through an alkoxycarbonyl-iminium intermediate, was less reactive than the ether **1**. Nevertheless, the bicyclic product **4** was obtained in 67% after 5 hours at 120 °C. To expand the synthetic utility of this reaction, we investigated the compatibility of frequently used carbamate protecting groups. The Fmoc- and CBz-protected compounds **5** and **7** are good substrates, affording the desired products in 56% and 68% yield, respectively. The piperidine-derived substrate **9** gave incomplete conversion under the standard conditions. The lower reactivity of α-C-H bonds of six-membered heterocycles has previously been observed by us and others in reactions that proceed via different mechanisms (e.g., metal insertion).[2] Increasing the catalyst loading to 10 mol% led to full conversion of the starting material and formation of the annulated product **10** in 63% isolated yield (Table 1, entry 5).

We next investigated the spirocyclization of ether substrates **11** and **13** (Table 1, entries 6 and 7). Although we expected higher reactivity of these substrates due to the greater hydride donor ability of the tertiary center, 5 mol% PtI_4 led to complete decomposition of the starting material under the optimized conditions. Monitoring the reaction by GC revealed that although the product was formed, it was rapidly decomposed prior to complete conversion of the starting material. Consequently, we turned to the less active platinum chlorides and found that K_2PtCl_4 was the optimal catalyst for these substrates, affording spirocycles **12** and **14** in 70% and 40%, respectively. It appears that the higher Lewis acidity of PtI_4 promotes the decomposition of the product via C-O bond cleavage, to afford a tertiary allylic carbocation and subsequent decomposition of this reactive intermediate. However, modulation of the catalyst activity by the choice of the halide ligand enabled us to expand the substrate scope. The less reactive pyrrolidine substrate **15** required the most active PtI_4 catalyst, furnishing interesting spiropyrrolidine product **16** in good yield (Table 1, entry 8). Presumably, spirocycle **16** is less prone to C-N bond cleavage, resulting in greater stability of this product under the catalytic conditions.

We have previously demonstrated the hydride donating ability of benzyl ethers.[3] We therefore prepared substrates **17** and **19**, which are readily available from the cyclohexene oxide, and in one step would provide complex bicyclic tetrahydrofurans. Substrate **17** led to the formation of product **18** in 62% yield, and although the yield is moderate, this reaction affords a single diastereomer of an attractive product. The brominated derivative **19** gave a lower yield of compound **20** (33%, Table 1, entry 10), showing the sensitivity of this reaction to electron-withdrawing substituents, particularly in the *para*-and *ortho*-position, due to destabilization of the oxocarbenium intermediate.

The HT-cyclization has a good substrate scope and enables the α-alkenylation of cyclic ethers and cyclic carbamates (with five- and six-membered rings), furnishing both the annulation and spirocyclization products. Also, formation of new heterocyclic rings, namely tetrahydrofurans, from the corresponding benzyl ethers was demonstrated. The reactivity of neutral platinum salts can be modulated by the choice of the halide ligand, which expands the scope to those substrates that yield sensitive products (e.g., substrates **11** and **13**). The scope is limited by the

requirement for a relatively rigid linker between the terminal alkyne and the α-position, and by the electronic effects that disfavor the hydride transfer by destabilizing the oxocarbenium intermediate. Attempts to cyclize non-activated internal alkynes failed to provide the desired products. For example, the methyl substituted derivative of substrate **1** proved to be largely unaffected by any of the platinum catalysts, even after prolonged heating at 150 °C.

Deuterium Labeling Studies and Proposed Mechanisms

To provide experimental support for the hydride transfer mechanism, we prepared the deuterium-labeled substrates **21** and **23** (Scheme 3). As expected, the benzyl deuterium was transferred to the vinyl position of product **22** with no loss of the label. However, the ^{1}H-NMR and the ^{2}H-NMR showed that a mixture of two isotopic stereoisomers was formed with the deuterium present in both vinylic positions (in a ratio close to 1:1, see Supporting Information). In the cyclization of **23**, the label in the acetylenic position is retained in the vinyl position of the product. In analogy to the previous case, with respect to the deuterium position in the alkene, the reaction is not stereospecific (Scheme 3). Some deuterium label was lost (62% deuterium incorporation in **24**), most likely due to the deuterium/hydrogen exchange at the acetylenic position, which is frequently observed with terminal alkynes.[8]

These results can be rationalized by two related mechanistic pathways, illustrated with substrate **21** in Scheme 4. In the pathway A, coordination of the catalyst activates the alkyne and triggers the hydride transfer, leading to the zwitterionic alkenyl intermediate VII. The alkenyl-platinum moiety then attacks the oxocarbenium ion, thereby forming the new C-C bond and the platinum carbene intermediate VIII. This species then undergoes a 1,2-hydrogen shift to furnish the product and the regenerated catalyst. The labeling results indicate that the last step, the 1,2-hydrogen migration and platinum salt elimination, is not stereospecific. Alternatively, the reaction may proceed via the pathway B where the platinum vinylidene IX is formed first,[6,7] followed by the through-space 1,6-hydride transfer to afford intermediate X, which affords the product via the sequence of C-C bond formation, non-stereospecific 1,2-hydrogen migration and platinum salt elimination. Similarly, conversion of the labeled substrate **23** to the product **24** can be explained by either pathway (not shown). Although the results with the labeled substrates support the hydride transfer mechanism, they do not distinguish between the two mechanisms, owing to, most probably, the lack of stereospecificity of the alkene formation step.

Conclusions

In summary, we have demonstrated that PtI_4 is an efficient Lewis acid catalyst for the hydroalkylation of unactivated alkynes with sp^3 C-H bonds in the context of saturated substrates. This method enables one-step preparation of complex heterocyclic compounds from readily available cyclic ethers and amines. In addition, we have shown that the activity of neutral platinum salts (PtX_n) can be modulated by the halide ligands. This modulation in turn allows for fine-tuning of the platinum center reactivity to match the reactivity and stability of chosen substrates and products. The scope of the through-space hydride transfer reactions has been expanded to include terminal alkynes as the hydride acceptors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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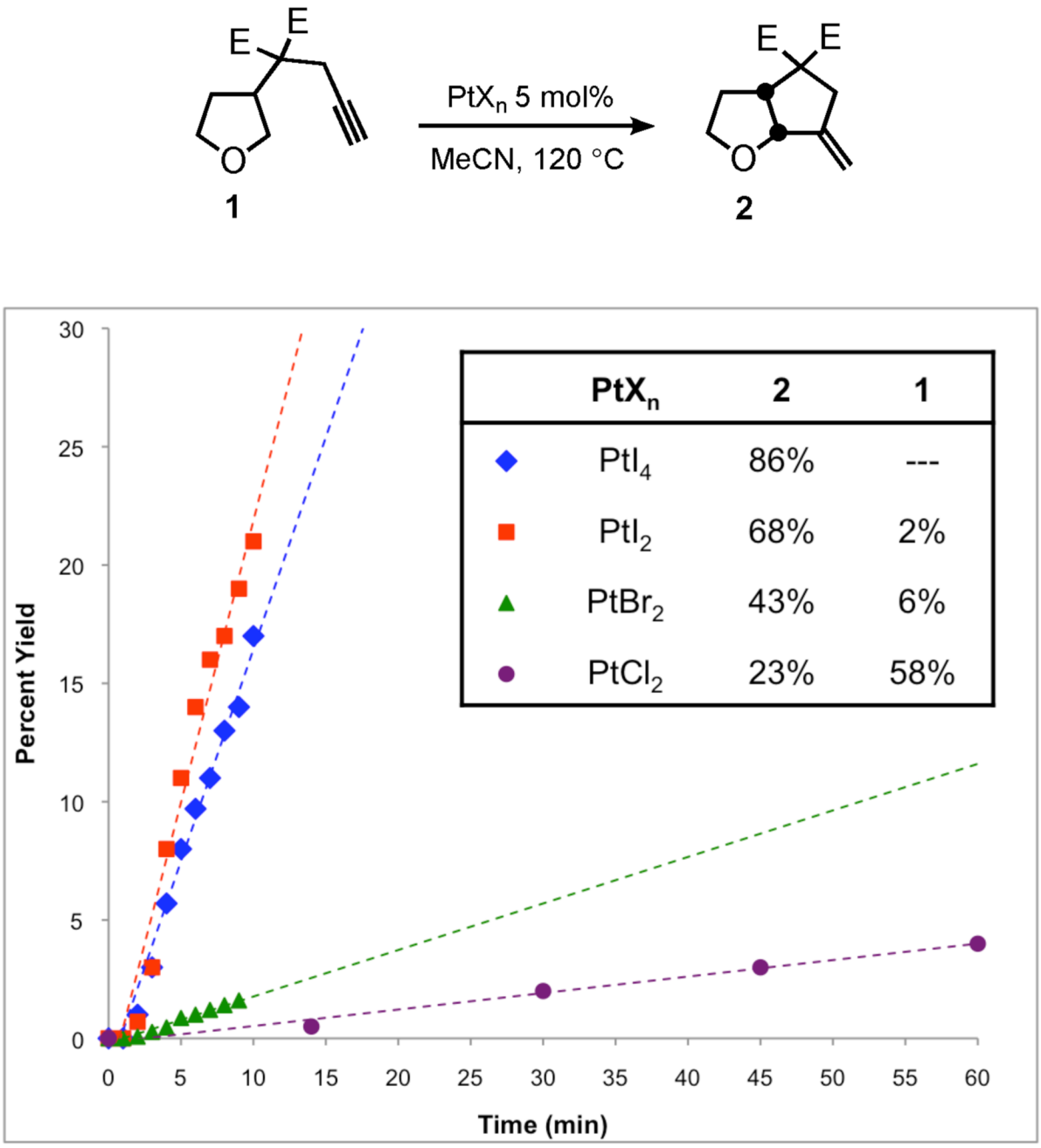
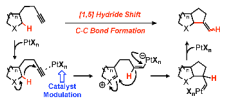
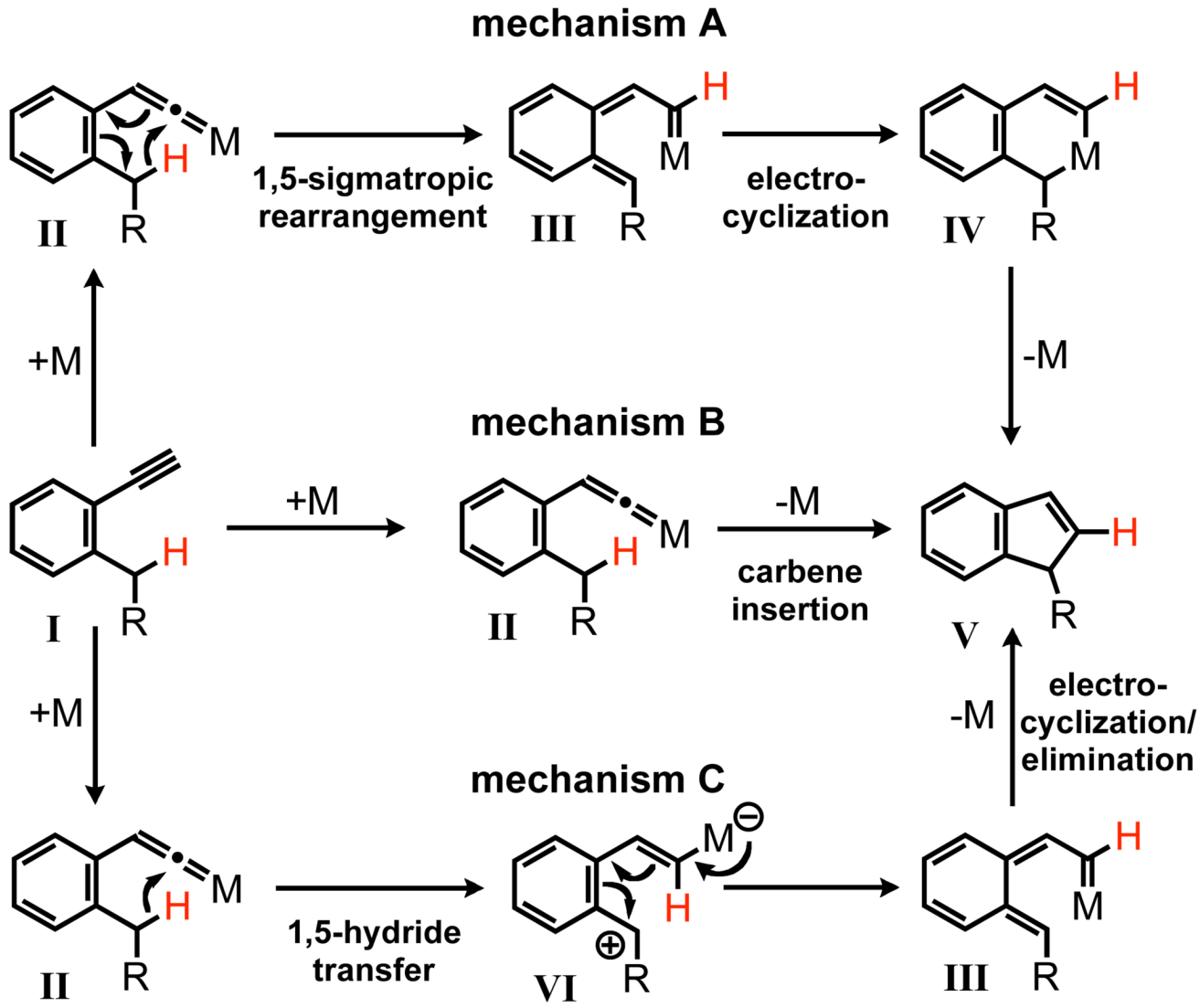


Figure 1.

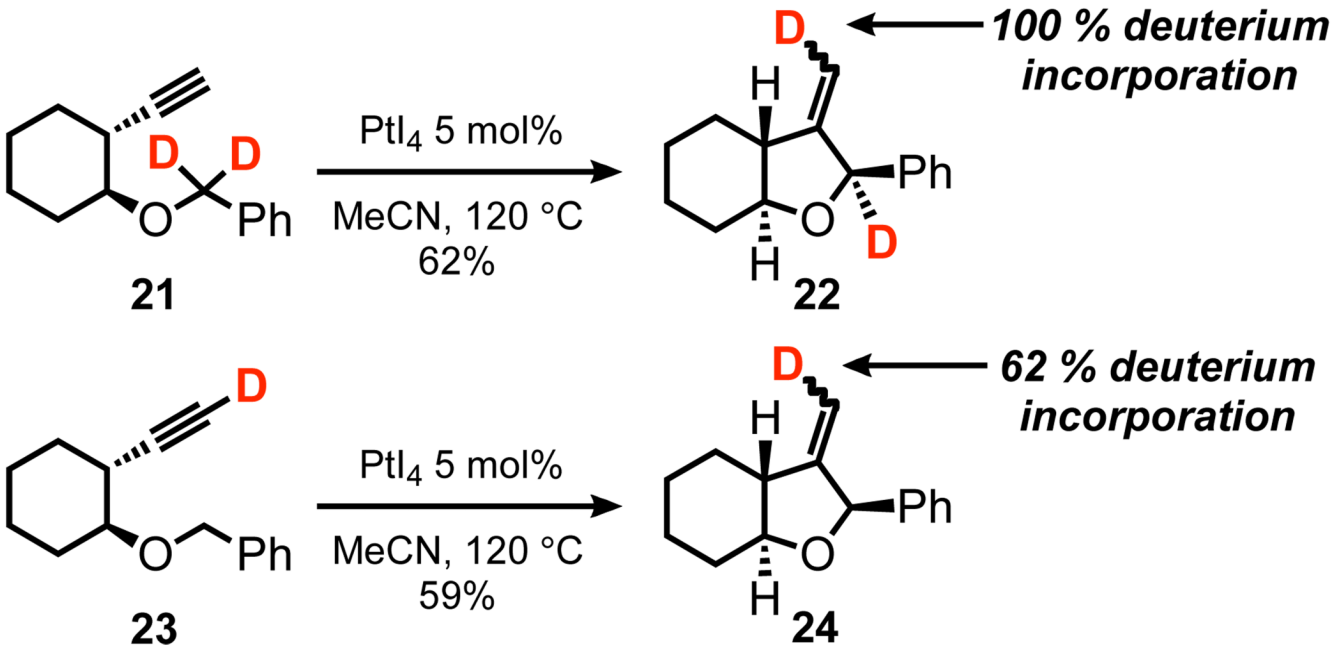
The Effect of Halide Ligand on the Catalyst Activity. Initial rates of product **2** formation are shown in the plot. The inset lists the yields of product **2** and remaining starting material **1**. Reactions performed at 0.05 M in dry MeCN. Yields were determined by GC, employing tetrachlorobenzene as an internal standard. E = CO_2Me.



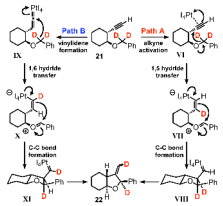
Scheme 1.
The Platinum-Catalyzed Coupling of Unactivated Alkynes and sp^3 C-H Bonds via the Through-Space Hydride Transfer



Scheme 2.
Cyclization of 2-Alkyl-1-ethynylbenzenes and Proposed Mechanistic Rationales



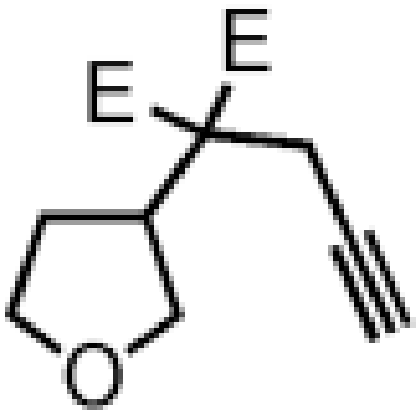
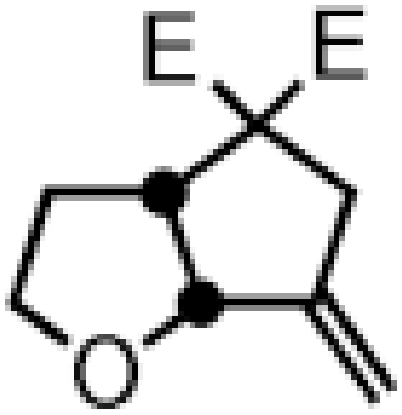
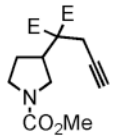
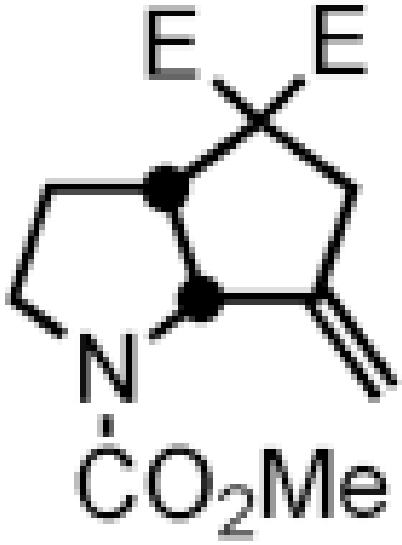
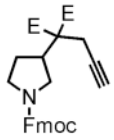
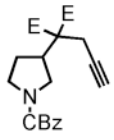
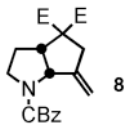
Scheme 3.
HT-Cyclization of Deuterium Labeled Compounds **21** and **23**

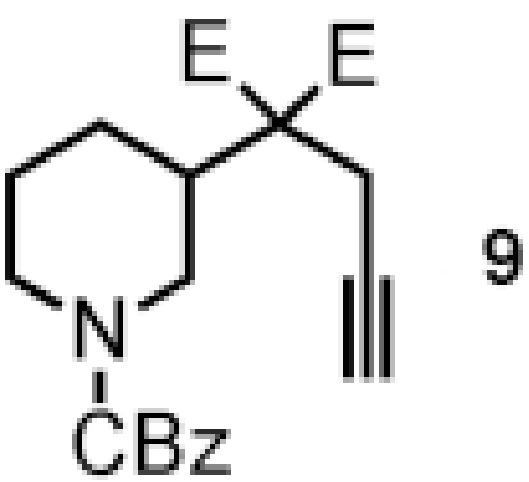
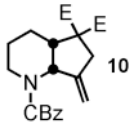
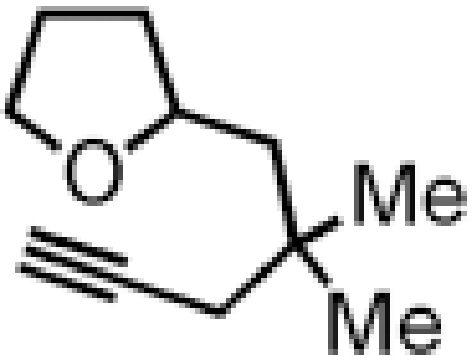
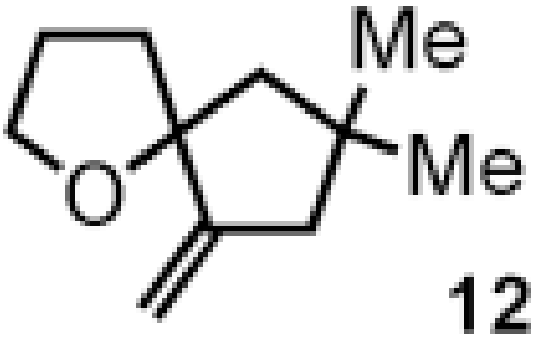
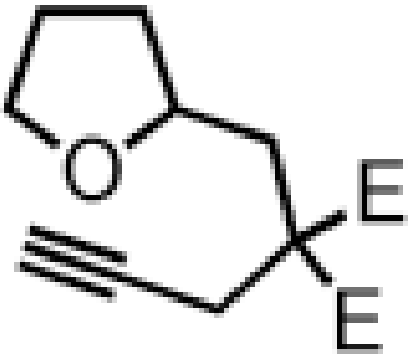
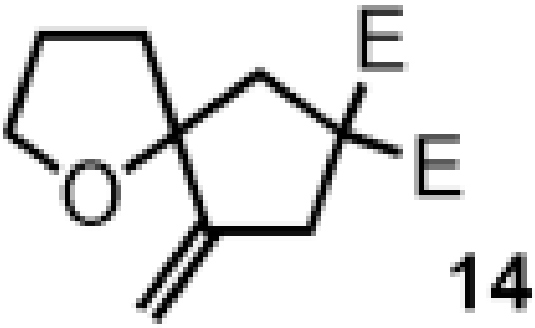


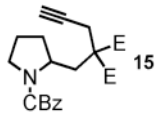
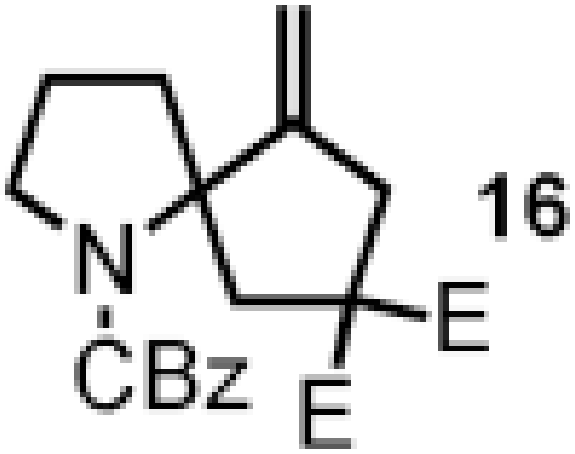
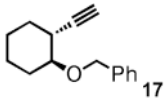
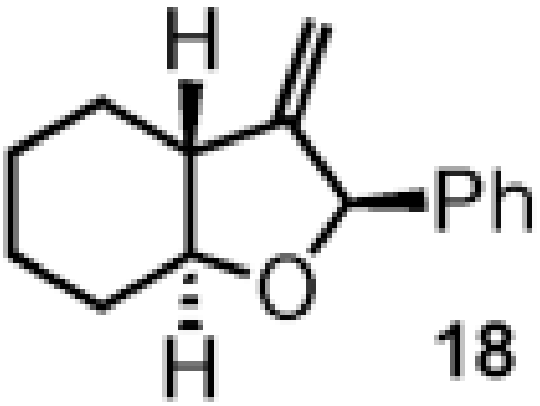
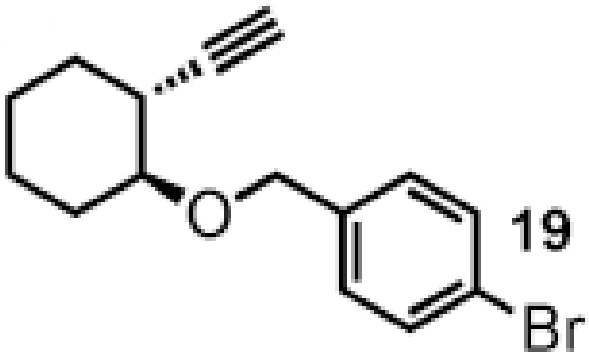
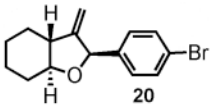
Scheme 4.
Proposed Mechanisms for the Platinum-catalyzed HT-cyclization

Table 1

Substrate Scope of the Platinum-Catalyzed HT-Cyclization[a]

entry	substrate[b]	prodouct[b]	time (h)	yi
1	 1	 2	3	8
2	 3	 4	5	6
3	 5	 6	6	5
4	 7	 8	7	6

entry	substrate[b]	prodouct[b]	time (h)	yi
5	 9	 10	5	63
6	 11	 12	12	70
7	 13	 14	12	40

entry	substrate[b]	prodouct[b]	time (h)	yi
8	 15	 16	9	7
9	 17	 18	12	6
10	 19	 20	12	3

[a] Reactions performed at 0.05 M in dry MeCN, employing PtI_4 5 mol% at 120 °C.

[b] E = CO_2Me.

[c] Isolated yield as an average of 3 runs.

[d] PtI_4 10 mol%.

[e] K_2PtCl_4 used in place of PtI_4.

[f] Relative geometry determined by NOESY NMR experiments.