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Transition-metal-promoted 6-*endo*-dig cyclization of aromatic enynes: rapid synthesis of functionalized naphthalenes

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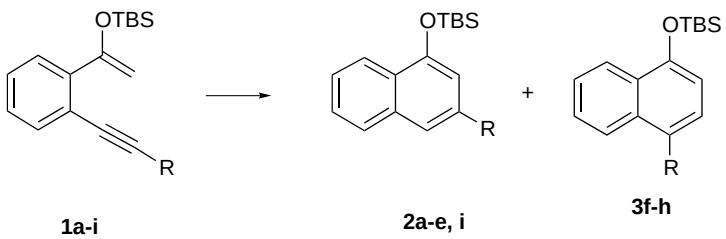
Abstract—Transition-metal-mediated cyclization of aromatic enynes provides high yields of substituted naphthalene compounds. The reaction can tolerate a wide range of substituents on both the olefin and the alkyne. The most useful catalysts were found to be $[Rh(CO)_2Cl]_2$, $PdCl_2$ and $PtCl_2$. In addition, a facile silyl migration occurs when the acetylene is substituted with a triorganosilyl group affording 4-silyl-naphthalenes. © 2001 Elsevier Science Ltd. All rights reserved.

The naphthalene ring system plays an important role in both natural product[1] and medicinal chemistry research.[2] As a result, new synthetic methods for the preparation of naphthalenes are an active area of research. In recent literature, several methods for the ring construction of polyaromatic compounds have been reported.[3] Many of the recent contributions to this field involve transition-metal-promoted ring construction. In 1996, Merlic described a procedure for the synthesis of polyarenes via an electrocyclization reaction of dienyne substrates.[4] In a related paper, Iwasawa reported the cyclization reaction of terminal aromatic enynes R = H (Scheme 1) mediated by $W(CO)_5$–THF.[5] Both of these reactions are believed to proceed through transition metal alkylidene complexes and are thus restricted to cyclization of terminal alkynes. In addition, Yamamoto recently reported a single example of an $EtAlCl_2$-mediated intramolecular addition of a silyl enol ether to an activated alkyne, which furnished the desired 1-naphthol in moderate yield.[6] Transition-metal-mediated reactions are becoming more prominent as methods for the synthesis of carbocyclic compounds since they allow C–C bond formation to occur between functionalities that otherwise are inert under conventional conditions.[7] Nucleophilic attack on transition metal π-activated alkyne complexes has also been documented in the literature.[8] Recently, Murai has disclosed the cyclization of π-activated alkynes with electron-rich aromatic nucleophiles.[9] In this letter, we report the construction of functionalized naphthalenes from various aromatic enyne substrates via an intramolecular 6-*endo*-cyclization mediated by a number of transition metal catalysts, including a stoichiometric version which is promoted by silver(I) salts.

Initial investigations were focused on determining which catalysts efficiently permit cyclization of silyl enol ether **1a**. A number of transition metal catalysts were surveyed, including Wilkinson's catalyst, which in the presence of silver salts, served only to cleave the silyl enol ether affording the corresponding ketone without any evidence of cyclization.



Scheme 1. Transition-metal-promoted cyclization of alkynyl silyl enol ethers **1a**–**i** (see Tables 1–3).

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Wender has recently demonstrated the synthetic value of $[Rh(CO)_2Cl]_2$ in transition-metal-mediated cycloaddition reactions.[10] Application of Wender's catalyst system to the current reaction resulted in clean cyclization to afford the desired TBS-protected naphthol **2a** in high yield (Table 1, entry 2). Cyclization also occurred at lower temperature (50 versus 90°C) under catalytic conditions using $[Rh(CO)_2Cl]_2$ providing the naphthol derivative **2a** in 93% yield (Table 1, entry 1). A ^1H NMR study revealed that using stoichiometric $[Rh(CO)_2Cl]_2$ in C_6D_6 at room temperature provided pure TBS-protected naphthol **2a**. No intermediates could be detected by ^1H NMR under these conditions. A control experiment was run without any catalyst by refluxing silyl enyne **1a** in toluene. This experiment resulted in complete recovery of starting material by ^1H NMR. Platinum(II) chloride as well as palladium(II) catalysts gave the desired cyclization product **2a** in high yield (Table 1, entries 3–5). During the course of our research, Murai reported the utility of $[RuCl_2(CO)_3]_2$ in carbocyclization reactions.[9] Application of this catalyst in the benzannulation reaction of the silyl enol ether **1a** at 80°C provided the desired product **2a**; however, about 10% unreacted starting material (**1a**) remained. It was determined that increasing the temperature to 130°C allowed smooth cyclization to occur furnishing **2a** in 93% yield (Table 1, entry 6). Catalytic amounts of silver trifluoroacetate gave low yields of the benzannulation product **2a** and resulted mainly in recovery of starting enol ether **1a**. Cyclization of **1a** ensued at room temperature if a stoichiometric amount of $Ag(OCOCF_3)$ is used in nitromethane (Table 1, entry 7). Cyclization of **1a** in the presence of catalytic amounts (5 mol%) of $AuCl_3$[11] also provided the naphthol derivative **2a** in an unoptimized 37% yield. Heating **1a** with 9 mol% $NiBr_2$ at 90°C gave a 1/1 mixture of the TBS-protected naphthol **2a** and starting material **1a**.

Table 1. Benzannulation of silyl enol ether **1a** ($R = n\text{-}C_6H_{13}$): catalyst optimization[12]

Entry	Conditions	% Yield (**2a**)
1	9 mol% $[Rh(CO)_2Cl]_2$, PhMe, 50°C	93
2	5.5 mol% $[Rh(CO)_2Cl]_2$, PhMe, 90°C	86
3	8 mol% $PtCl_2$, PhMe, 90°C	94
4	10 mol% $PdCl_2$, PhMe, 90°C	87
5	10 mol% $Pd(PhCN)_2Cl_2$, PhMe, 90°C	92
6	11 mol% $[RuCl_2(CO)_3]_2$, PhMe, 130°C	93
7	1.1 equiv. $Ag(OCOCF_3)$, $MeNO_2$, rt	76

The use of $RhCl_3$ and $CpRu(PPh_3)_2Cl$ resulted in recovery of the silyl enol ether **1a** with no apparent ring closure occurring at 90°C. Benzannulation of **1a** with $Rh(CO)_2(acac)$ or $[RuCl_2(p\text{-cymene})]_2$ at 100°C afforded a mixture of starting material (**1a**) and the corresponding cyclized product **2a** (7/1 **1a**/**2a** for Rh catalyst and 4.5/1 **1a**/**2a** for the Ru catalyst). The cationic copper catalyst, $Cu(MeCN)_4PF_6$ provided a complex and uncharacterized mixture of products with no evidence of the desired naphthalene **2a** being formed by ^1H NMR.

In the synthesis of TBS-protected naphthols **2**, the steric bulk of the substituent on the alkyne was varied from R = H to R = *t*-Bu. Silyl enol ethers **1a**–**e**,**i** with R = Me, Bn, *n*-hexyl, and Ph cyclized smoothly providing the desired TBS-protected naphthols in 71–89% yield (Table 2, entries 2–5). The unsubstituted alkyne **1i** also cyclized; however, the yield was lower than the alkyl substituted systems (Table 2, entry 1). In general, the sterically more demanding groups, such as *t*-butyl, required higher temperatures for complete cyclization to occur. In the $[Rh(CO)_2Cl]_2$ (10 mol%)-mediated cyclization of the *t*-butyl silyl enol ether **1e** at 130°C a 1/1 mixture of the cyclization product **2e** and silyl enol ether **1e** was obtained in a combined yield of 68%. The $PtCl_2$ catalyst at 140°C (Table 2, entry 6) resulted in efficient ring closure of **1e**; however, reaction at lower temperature and catalyst loading resulted in incomplete conversion (10 mol% $PtCl_2$, PhMe, 100°C, 2.1/1 mixture **2e**/**1e**, 66% combined yield). Benzannulation of **1e** at 130°C furnished a 4.2/1 mixture of **2e** and **1e** with 10 mol% $PtCl_2$ catalyst.

The silyl alkynes (**1f**–**h**) also afforded TBS-protected naphthol products (**2f**–**h** and **3f**–**h**); however, in the case of the rhodium complex, $[Rh(CO)_2Cl]_2$, silyl migration from C3 to C4 was observed. The structure of the TMS naphthol **3f** was verified by conversion of the known 4-bromo-1-naphthol[13] to the 4-trimethylsilylnaphthol derivative **3f**. In addition the coupling constant between protons at C2 and C3 ($J_{2,3} = 7.55$ Hz) also indicates migration of the trimethylsilyl group. All three silyl substrates (**1f**–**h**) reacted efficiently with C3 to C4 silyl migration with the organorhodium complex, $[Rh(CO)_2Cl]_2$. Reaction of the silyl substrates (**1f**–**h**) with 10–15 mol% $PtCl_2$ at 100–130°C provided mixtures of products. The more sterically hindered substrates required higher temperatures and catalyst loadings for complete consumption of the starting material. From careful ^1H NMR analysis the C3 and

Table 2. Transition metal cyclization with variation of the alkyne substituent

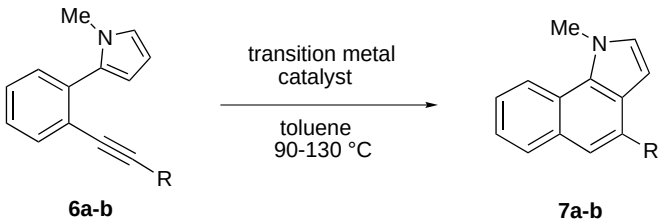
Entry	Enol ether	R	Conditions	% Yield (**2**)
1	**1i**	H	10 mol% $[Rh(CO)_2Cl]_2$, PhMe, 110°C	51
2	**1b**	Me	10 mol% $[Rh(CO)_2Cl]_2$, PhMe, 110°C	89
3	**1c**	CH_2Bn	10 mol% $[Rh(CO)_2Cl]_2$, PhMe, 110°C	71
4	**1c**	CH_2Bn	1.1 equiv. $Ag(OCOCF_3)$, $MeNO_2$, rt	75
5	**1d**	Ph	10 mol% $[Rh(CO)_2Cl]_2$, PhMe, 100°C	79
6	**1e**	*t*-Bu	17 mol% $PtCl_2$, PhMe, 140°C	56

C4 silyl naphthol derivatives were found to be the major cyclization products; however, trace amounts of 1-dimethyl-*tert*-butylsilyloxynaphthalene from proto-desilylation, was also produced with R = TMS and TBS. Cyclization of **1g** with $PtCl_2$ afforded only the silylated naphthol derivatives (**2g** and **3g**) with no traces of the proto-desilylated compound found in the crude reaction mixture. In the case of the Pt(II)-mediated cyclization, some cleavage of the TBS silyl enol ether **1f–h** had occurred providing the corresponding methyl ketone of **1**. 2,6-Di-*t*-butyl-4-methylpyridine (1.1 equiv.) was added to the reaction mixture containing 15 mol% $PtCl_2$ and silyl enol ether **1g** with the hope that it would minimize both the amount of silyl enol ether hydrolysis as well as the *C*-desilylation; however, ^1H NMR analysis indicated that a mixture of cyclized compounds (C3-TBS, C4-TBS and *C*-desilylated naphthol) and the acetophenone derivative were formed under these conditions.[14] In general, with $PtCl_2$, the major cyclization adducts were the non-migrated compounds **2f** and **2h**. Cyclization of **1g** with $PtCl_2$ provided a nearly 1/1 mixture of the C3 and C4 silyl naphthol derivatives (**2g** and **3g**). Cyclization of the TMS derivative **1f** with 1.05 equiv. $Ag(OCOCF_3)$ resulted in a mixture of the silyl enol ether **2f** and the acetophenone derived from **1**. Palladium(II) catalysts ($PdCl_2$ and $PdCl_2(PhCN)_2$) did not provide any of the desired cyclization products with the silyl alkynes (**1g–h**).

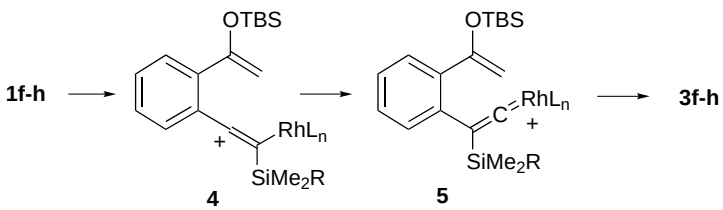
A proposed mechanism of the silyl migration utilizing $[Rh(CO)_2Cl]_2$ is shown in Scheme 2. The key feature of this rearrangement involves the silyl migration of **4** producing the rhodium carbene complex **5**, which cyclizes to the final product **3f–h**. As can be seen from the data in Table 3, silyl migration improves as the steric bulk of the silyl group increases. Thus, the driving force for the silyl rearrangement is probably to relieve the non-bonded interactions between the RMe_2Si group and RhL_n in intermediate **4**.

Expanding the synthetic method to compounds bearing other electron-rich, unsaturated functionalities such as a 2-substituted pyrrole is illustrated in Table 4. Cyclization of pyrrole **6a**,**b** with either $[Rh(CO)_2Cl]_2$, $PtCl_2$ or $AuCl_3$[11] provided high yields of the cyclization products **7a**,**b** (Scheme 3).

In addition, a control experiment was performed under thermal conditions without any catalyst. Thus, heating the alkyne **6a** in refluxing toluene for 14 h, followed by analysis of the crude reaction mixture, indicated that no reaction had taken place by ^1H NMR.



Scheme 3. Transition metal cyclization of alkynyl pyrroles **6a**,**b**.



Scheme 2. A proposed mechanism for the silyl rearrangement of **1f–h**.

Table 3. Rearrangement of silyl alkynes **1f–h**

Entry	Enol ether	R	Catalyst	C4:C3 (NMR)	% Yield (**3**)
1	**1f**	$SiMe_3$	10 mol% $[Rh(CO)_2Cl]_2$, 90°C	4.9/1	75
2	**1g**	$SiMe_2Ph$	10 mol% $[Rh(CO)_2Cl]_2$, PhMe, 130°C	5.2/1	80
3	**1h**	$SiMe_2t$-Bu	13 mol% $[Rh(CO)_2Cl]_2$, PhMe, 130°C	7.4/1	91

Table 4. Carbocyclization of alkynyl pyrroles **6a**,**b**[15]

Entry	Substrate	R	Conditions	% Yield (**7**)
1	**6a**	Me	10 mol% $[Rh(CO)_2Cl]_2$, 90°C	75
			9 mol% $PtCl_2$, 90°C	94
			1.1 equiv. $Ag(OCOCF_3)$, $MeNO_2$, rt	69
2	**6b**	n-C_6H_{13}	10 mol% $AuCl_3$, PhMe, 100°C	97
			13 mol% $PtCl_2$, PhMe, 110°C	77
			13 mol% $[Rh(CO)_2Cl]_2$, PhMe, 130°C	80

In summary, the intramolecular transition-metal-mediated cyclization of acetylenic silyl enol ethers[16] and pyrroles[17] constitutes an efficient method for the construction of substituted naphthalenes. The reaction is promoted by a number of catalysts and has a wide synthetic scope. In addition, $[Rh(CO)_2Cl]_2$-catalyzed cyclization of organosilyl alkynes provides a unique pathway to C4 silyl rearranged naphthalene derivatives in high yield.

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12. The silyl enol ethers **1** were prepared from *o*-bromoacetophenone by Pd-mediated cross-coupling with the appropriate alkyne followed by silyl enol ether formation with TBSOTf (1.05 equiv.) and TEA (5 equiv.) in dichloromethane. For key references, see: (a) Traditional Sonogashira conditions for the palladium coupling were utilized for the preparation of compounds **1a**–**c** and **1f**. See references 3a and 5b; (b) The silyl alkynes (**1g**–**h**) were coupled by a modified Fu–Buchwald procedure using a higher catalyst loading (6 mol% $PdCl_2(PhCN)_2$ and 12.4 mol% P(*t*-Bu)$_3$) and 2.0 equiv. alkyne, see: Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729–1731. Compounds **1d**,**e** were best prepared by a Negishi coupling of *o*-bromoacetophenone and the alkynylzinc chloride with 5–15 mol% $Pd(PPh_3)_4$. The silyl enol ethers were prepared as described above.
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14. $PtCl_2$ cyclization of **1g** (R = $SiPhMe_2$) provided a 1/1.06/1.91/2.47 mixture of acetophenone/silyl enol ether/C3 silyl naphthol/C4 silyl naphthol. Cyclization of **1f** (R = TMS) provided a 2.18/1.17/1.00 mixture of C3 silyl naphthol/C4 silyl naphthol/*C*-desilylated naphthol. Cyclization of **1h** (R = TBS) with $PtCl_2$ provided a complex mixture of products comprised of a 2.16/1.12/3.68/1.00/1.60 of acetophenone/silyl enol ether/C3 silyl naphthol/C4 silyl naphthol/*C*-desilylated naphthol. In the presence of 2,6-di-*t*-butyl-4-methylpyridine furnished a 4.72/4.05/1.00/2.32 mixture of acetophenone/C3 silyl naphthol/C4 silyl naphthol/*C*-desilylated naphthol derivative.
15. The alkynyl pyrroles **6a**,**b** were prepared from 1-bromo-2-iodobenzene by a Sonogashira and Negishi coupling procedures. See reference 5b.
16. Typical procedure (Table 1, entry 3): cyclization of **1a** (R = *n*-C_6H_{13}). To a toluene (15 mL) solution of the silyl enol ether **1a** (63.6 mg, 0.186 mmol) was added $PtCl_2$ (3.9 mg, 0.015 mmol) under Ar. The resulting mixture was heated at 90°C (oil bath temperature) for 15 h. The reaction mixture was cooled to rt and concentrated under vacuum. Crude ^{1}H NMR indicated formation of the desired product in >95% purity. Purification was accomplished by silica-gel chromatography (1/4 ethyl acetate–hexane) to afford 60.0 mg of product **2a** (94% yield).
17. Typical procedure (Table 4, entry 2): cyclization of **6b**. To a toluene (13 mL) solution of the pyrrole **6b** (106.5 mg, 0.402 mmol) was added $[Rh(CO)_2Cl]_2$ (21 mg, 0.054 mmol) under Ar. The resulting mixture was heated at 130°C (oil bath temperature) for 15 h. The reaction mixture was cooled and concentrated under reduced pressure. Crude ^{1}H NMR indicated formation of the desired product **7b**. Purification was accomplished by preparative thin-layer chromatography (silica gel, 3% ether–hexane) to afford 85.2 mg of product **7b** (80% yield).