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A Rhodium(I)-Catalyzed Demethylation–Cyclization of *o*-Anisole-Substituted Ynamides in the Synthesis of Chiral 2-Amido Benzofurans§

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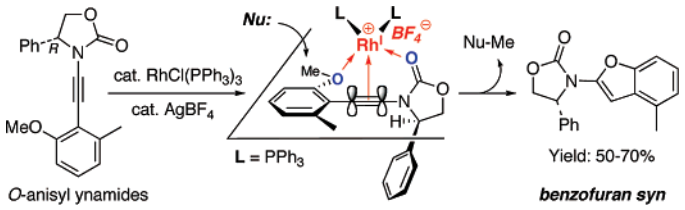
ABSTRACT



A Rh(I)-catalyzed demethylation–cyclization sequence for a direct transformation of *o*-anisole-substituted ynamides to benzofurans is described here. The Ag salt functions synergistically with Rh(I) for the key demethylation step.

Benzofurans represent one of the most important heterocyclic pharmacophores in medicinally and biologically relevant entities.[1−4] We recently reported[5] a Rh(I)-catalyzed [2 + 2 + 2] cycloaddition of aryl-terminated ynamides[6−9] as a stereoselective approach to the synthesis of *N*,*O*-biaryls [see **1** → **3** in Scheme 1].[10−12] In our work, Ag salts were employed as a key additive to enhance the catalytic efficiency

§ With deepest appreciation and respect, this paper is dedicated to Professor Gilbert Stork on the special occasion of his 85th Birthday.

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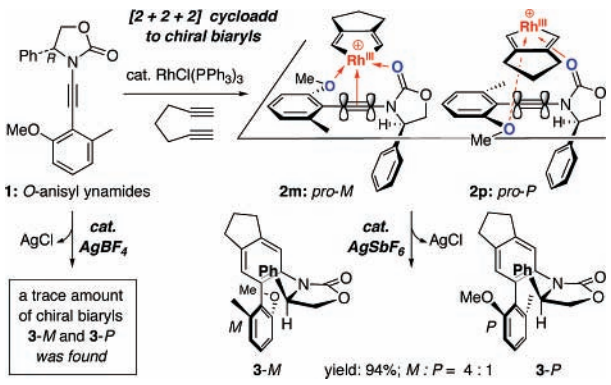
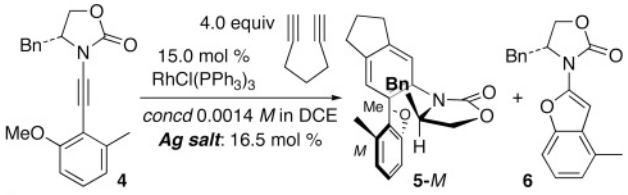
Scheme 1. Effects of Ag-Salt Additives in the [2 + 2 + 2] Cycloaddition



of Wilkinson's catalyst through the counteranion effect in which the rhodium metal is rendered cationic with the chloride anion being stripped, leaving behind softer anions such as $[SbF_6]^-$ and open valence.[13] However, intriguingly, not all Ag salts had the same effect. We found that the utility of $AgBF_4$ led to a very different outcome with only a small amount of desired chiral biaryls **3**-*M*/*P*. We have since then identified this intriguing reaction pathway, and herein, we report a Rh(I)-catalyzed demethylation−cyclization sequence in the synthesis of de novo benzofurans.

When *o*-anisole-substituted ynamide **4** was subjected to conditions that were optimized for the [2 + 2 + 2] cycloaddition reaction with 1,6-diyne employing 15.0 mol % of the Wilkinson' catalyst (Table 1), we found that the

Table 1. Benzofuran Formation in the Presence of $AgBF_4$



entry	*Ag salts*	temp [°C]	time [h]	convn [%][a]	ratio: **5 : 6**[a]
1	none	rt	16	5	5 : 0
2		85	3	20	20 : 0
3		85	30	77	76 : 1
4	AgOTf	rt	16	48	24 : 24
5		85	3	83	68 : 16
6		85	30	98	71 : 27
7	$AgSbF_6$	rt	16	57	47 : 10
8		85	3	89	81 : 8
9		85	30	100	85 : 15
10	$AgPF_6$	rt	16	50	36 : 14
11		85	3	100	81 : 18
12	$AgBF_4$	rt	16	100	17 : 83

[a] Determined by LCMS.

addition of a Ag salt not only played a critical role in the rate of conversion in leading to biaryl **5** (entries 1−3),[13] but it also provided a byproduct (entries 4−12). This unexpected new product was unambiguously assigned as benzofuran **6**[14] through the X-ray crystal structure of a related benzofuran product **7** (Figure 1).

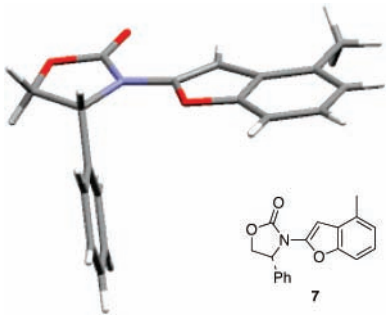


Figure 1. X-ray structure of benzofuran **7**.

Under these conditions, the formation of the benzofuran side product appears to be dependent upon the nature of the salt in which $AgBF_4$ provided the fastest consumption of the starting ynamide **4** (entry 12) relative to AgOTf (entries 4−6), $AgSbF_6$ (entries 7−9), and $AgPF_6$ (entries 10 and 11), while providing the best chemical yield for **6**. This dichotomy, as delineated in Scheme 2, intrigued us.

The complex **8**, which consists of a bidentate coordination of the ynamide motif to the rhodio-cyclopentadienyl intermediate, had been proposed[5] as an intermediate en route to chiral biaryl **5**-*M*. While this represents one of the generally accepted [2 + 2 + 2] cycloaddition pathways,[15] and while a silver salt is known to enhance the coordination ability of the rhodium metal[13] by stripping away the chloride ligand, the subtle difference between SbF_6^- [or OTf^- or PF_6^-] and

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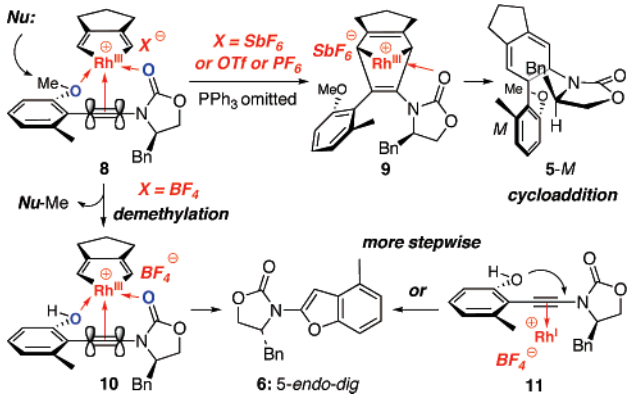
Scheme 2. Demethylation versus Cycloaddition



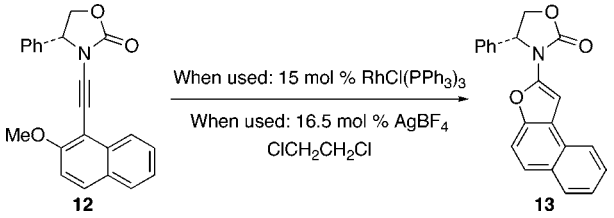
BF_4^- is provoking with the latter favoring a 5-*endo-dig* cyclization pathway through the intermediacy of **10** (or **11**) after the initial demethylation.

We remain uncertain of this aforementioned dichotomy. However, as well precedented as 5-*endo-dig* cyclizations from *o*-hydroxyphenylacetylenes are in the synthesis of benzofurans,[3,16−18] a tandem sequence of dealkylation−cyclization via *o*-anisole acetylenes is relative less common.[19] Thus, we elected to examine this reaction in greater detail, for it represents an excellent catalytic protocol for such transformation.

As shown in Table 2, by using ynamide **12** as the model, it became evident that (1) Wilkinson's catalyst by itself is not useful in the benzofuran formation (entry 1) and the presence of $AgBF_4$ is critical (entry 3) and (2) adventitious H_2O[20] is likely the nucleophile that carries out the demethylation, as the addition of 4 Å MS retards the reaction (entry 1 versus 2, and 3 versus 4, and 5 versus 6).

More importantly, it appears that $AgBF_4$ and Wilkinson's catalyst function synergistically to provide a more effective demethylation−cyclization, leading to benzofuran **13** in much higher yield (entry 3 versus 5). This result suggests that $AgBF_4$ and Wilkinson's catalyst could in fact provide a unique catalytic system for the demethylation and cyclization process of *o*-anisole-substituted ynamides. To verify this implication, we examined a series of commonly used Lewis acids for demethylating methyl ethers.

Table 2. The Importance of Rh(I) Cat., $AgBF_4$, and H_2O

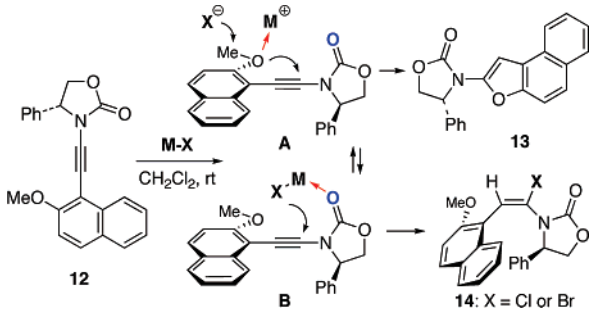


entry	Rh(I)	Ag(I)	4 Å MS	time [h]	temp [°C]	yield [%][a] **12**[b]	yield [%][a] **13**
1	√			24	25 to 85	90	nd[c]
2	√		√	24	25 to 85	95	nd
3		√		**12**	**25**	**5**	**25**
4		√	√	48	25 to 85	50	trace
5	√	√		**12**	**25**	**5**	**54**
6	√	√	√	24	25	75	trace

[a] Isolated yields. [b] Recovered ynamide **12**. [c] nd: not determined.

As shown in Table 3, we found that other than $MgBr_2$, which provided formation of the desired benzofuran **13** but at a much higher temperature, all other Lewis acids did not lead to **13** but to halo-enamide **14**-Cl or **14**-Br in favor of

Table 3. Limited Demethylation under Other Lewis Acidic Conditions



entry	MX	time [h]	temp [°C]	yield [%][a] **12**	yield [%][a] **13**	**14**-Cl	**14**-Br	*E*:*Z*
1	$TiCl_4$	2	0	0	0	24		7.5:1
2	$AlCl_3$	24	0	0	0	0		
3	BCl_3	1.5	0	0	0	35[b]		25:1
4	BCl_3	60	25	0	0	0[b]		
5	TMSCl	48	25	25	0	54		14:1
6	TMSCl	48	85	0	0	93		19:1
7	$MgCl_2$	72	85	22	0	73		17:1
8	BBr_3	1.5	0	0	4		8	7:1
9	$MgBr_2$	120	25	25	trace		58	8:1
10	$MgBr_2$	12	85	10	45		26	

[a] Isolated yields. [b] For entry 3: A chloro aminal byproduct was isolated in 18% yield (see the Supporting Information and ref 22). For entry 4: The chloro aminal product was found in 33% yield.

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(19) For recent examples in dealkylation−cyclization via *iodine* see: (a) Yao, T.; Yue, D.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 9985. (b) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 10292. (c) Arcadi, A.; Cacchi, S.; di Giuseppe, S.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2002**, *4*, 2409. Via *mercury*: (d) Kao, C.-L.; Chern, J.-W. *Tetrahedron. Lett.* **2001**, *42*, 1111. Via *platinum*: (e) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024. (f) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022.

(20) We are in the process of quantifying the significance of H_2O in this process.

the *E*-isomer. While additional Lewis acids could be tried, these preliminary results are sufficient to suggest that a demethylation simply through intermediate **A** is not a trivial task with Lewis acids likely preferring the more Lewis basic urethane carbonyl oxygen shown in **B**, which would lead to the halo-enamide formation.[21]

Given these comparisons, it is reasonable to suggest that the demethylation does involve the Rh metal through the complex **D** in which *only* the cationic Rh metal, after being stripped of the Cl ligand present in complex **C**, could possess additional coordination sites for a bidentate complexation with the *o*-methoxy oxygen in **D** (in blue and see the red arrow in Figure 2). This would in turn set up for the key

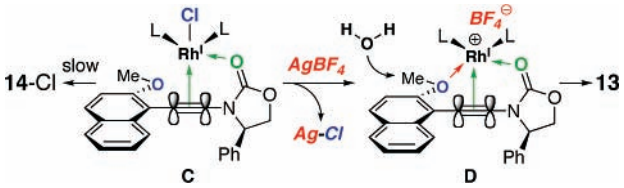

Figure 2. A proposed mechanistic pathway to benzofuran.

demethylation en route to benzofuran **13**. It is noteworthy that without the addition of $AgBF_4$, **14**-Cl was also found, although in low yield. It is likely formed from the complex **C**, thereby further underscoring the significance of the silver salt additive.

With these mechanistic insights in hand, the generality is shown in Figure 3 for the synthesis of various chiral 2-amido benzofurans from a range of ynamides. It is also noteworthy that in the absence of any diynes, other silver salts such as $AgSbF_6$ are now also feasible. Our protocol essentially renders *o*-anisole-substituted ynamides as a protected or latent benzofuran motif. These 2-amido benzofurans should be

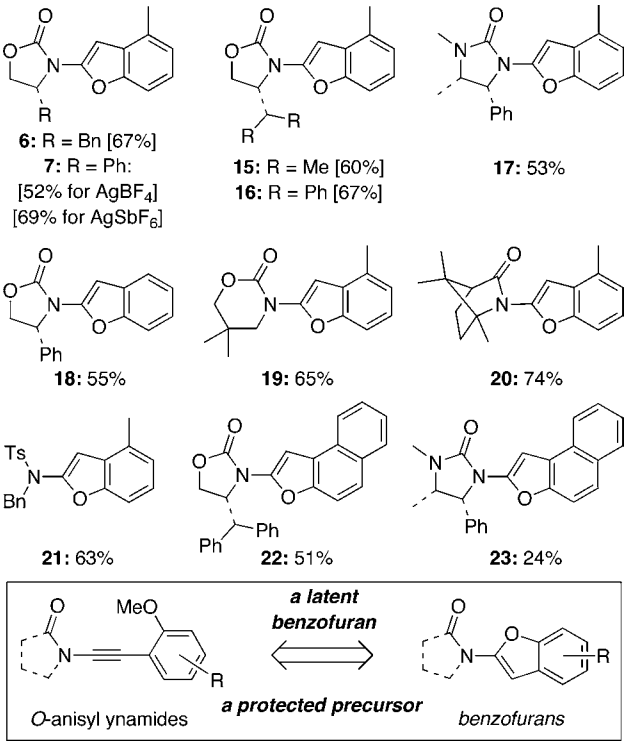

Figure 3. A Rh(I)-Catalyzed Demethylation-Cyclizations. For reaction conditions, see the Supporting Information and ref 23.

useful as chiral templates for further stereoselective transformations[24] as well as potential applications in the synthesis of benzofuran-related natural products.[25]

We have described here an unexpected Rh(I)-catalyzed demethylation−cyclization sequence for the synthesis of benzofurans from *o*-anisole-substituted ynamides. The silver salt is critical for the demethylation and functions synergistically with the rhodium catalyst to form a unique catalytic system feasible for a demethylation−cyclization sequence that is a much less used synthetic route to benzofurans directly from *o*-methoxyphenylacetylenes.

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Supporting Information Available: Experimental details, characterization data, X-ray structural analysis, and NMR spectrl for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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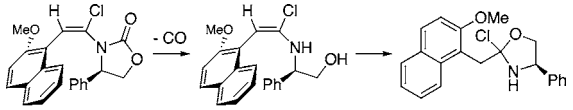
(22) The chloro aminal byproduct **ii** isolated here as a single isomer is likely derived from the initial formation of chloro-enamide **14**-Cl. Characterizations of **ii** is in the Supporting Information but the relative stereochemistry of the aminal carbon was not assigned.



(23) **General Procedure.** A solution of $RhCl(PPh_3)_3$ (15.0 mol %) and $AgBF_4$ or $AgSbF_6$ (16.5 mol%) in anhyd CH_2Cl_2 was stirred at rt for 30 min. The respective *o*-anisole-terminated ynamide was then added as a solid to the reaction mixture, and the reaction was stirred at rt and followed via TLC. After the reaction was complete, the solution was filtered through a short pad of silica gel and the filtrate was concentrated in vacuo. Purification of the crude residue by silica gel flash column chromatography (25% EtOAc in hexanes) yielded the desired benzofuran **7** in 52% and 69% yield respectively for $AgBF_4$ and $AgSbF_6$.

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