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Enantioselective *O*- and *N*-Nitroso Aldol Synthesis of Tin Enolates. Isolation of Three BINAP−Silver Complexes and Their Role in Regio- and Enantioselectivity

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One of the most intensely studied areas in chemical synthesis at present is the development of new catalytic and highly enantioselective processes, especially for the efficient synthetic construction of α-oxy and α-amino carbonyl compounds.[1] After our early study of nitroso aldol synthesis,[2] we had demonstrated that the BINAP−silver complex is an effective catalyst for the *O*-nitroso aldol synthesis of tin enolates.[3] In this Communication, we describe the isolation of three structures of BINAP−silver complexes identified by NMR study and X-ray analysis.[4] Furthermore, each of the three complexes plays a different role in regio- and enantioselectivity in the nitroso aldol synthesis (Scheme 1).

In an effort to investigate the coordination of BINAP−silver metal, low-temperature NMR studies were undertaken. In the preparation of 1 equiv of AgOTf for (*R*)-BINAP in THF, the catalyst was unambiguously discerned as a mixture of three species, 1:2 (**A**), 1:1 (**B**), 2:1 (**C**) (AgOTf·(*R*)-BINAP) complexes, in the ^{31}P NMR spectrum at −78 °C (molar ratio of three complexes: **A**/**B**/**C** = 21/63/16).[5] We were very pleased to learn that, during a systematic survey of the metal-to-ligand ratio, either the **A** or the **C** complex was selectively generated from 2 equiv of (*R*)-BINAP or 0.4 equiv of (*R*)-BINAP for AgOTf, respectively. The generation of the 1:1 complex was highly dependent on the choice of silver anion, but, fortunately, this complex was also obtained almost exclusively by switching the silver salt from AgOTf or $AgClO_4$ to AgOAc or $AgOCOCF_3$. Furthermore, we were able to isolate each metal species, and the X-ray crystallographic study provided us a clear view of the structure of each catalyst.[6] The tetragonal geometry of complex **A** (X = OTf) conformed to that of the proposed structure previously reported by our lab.[7] The tetragonal geometry of complex **B** (X = $OCOCF_3$) is likewise similar to that of a closely related X-ray structure of BINAP·AgOAc reported by Yamagishi et al., with silver coordinated to two oxygen atoms. The crystallographic data for complex **C** (X = OTf) revealed a trigonal geometry, but with a metal center coordinated to one phosphine and triflate on another silver salt.[8]

Given each of the silver−BINAP complexes, **A**, **B**, **C** via the proper combination of metal/ligand ratio and/or choice of metal salt, a representative selection of tin enolates was evaluated in the *O*-nitroso aldol process. The reaction with the trimethyltin enolate of cyclohexanone in the presence of 10 mol % of catalyst derived from (*R*)-TolBINAP and AgOTf (THF, 1 h, −78 °C) afforded *O*-adduct with exceptional regio- and stereoselectivity (*O*-/*N*- = >99:1, >99% ee). The AgOAc- or $AgOCOCF_3$-derived 1:1 complexes **B** should also be efficient catalysts that exhibit the capacity to participate in the activation as a Lewis acid uniformly to give high enantioselectivities and efficiencies (95−97% ee, 93−94% yield) under the relatively low catalyst loading (Table 1). In contrast to these results, reaction with complex **C** afforded the *O*-adduct in low enantioselectivity (*O*-/*N*- = 95:5, 9% ee). Further, complex **A** was totally ineffective in producing the *O*-adduct (>99% *N* selective) with <1% ee and thus did not contribute to the nitroso aldol reaction. Taken into account all of the above results, it appears that 1:1 complex **B** should be the responsible catalyst for the silver catalyzed *O*-nitroso aldol process as evidenced by the enantioselectivity/regioselectivity profile.

Scheme 1

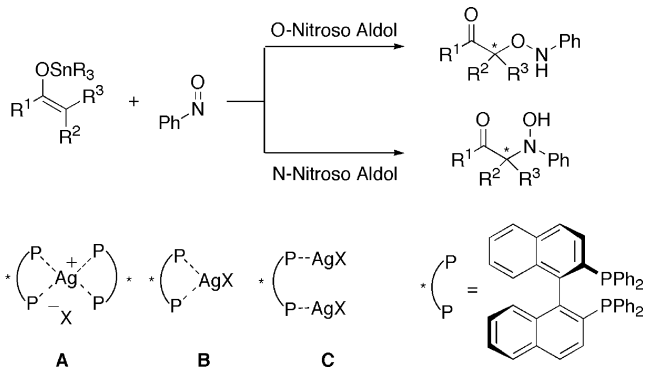
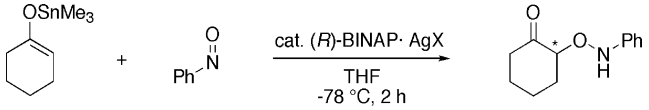


Table 1. 1:1 (AgX·(*R*)-BINAP) Complexes in *O*-Nitroso Aldol Synthesis[a]



entry	mol %	AgX	yield, %[b]	ee, %[c]
1[d]	10	AgOTf	88	99
2	2	AgOAc	93	97
3	2	$AgOCOCF_3$	94	95

[a] Reactions were conducted with a catalytic amount of (*R*)-BINAP·AgX, 1.0 equiv of nitrosobenzene, and 1.0 equiv of trimethyltin enolate in THF at −78 °C for 2 h. [b] Isolated yield. [c] Determined by HPLC (Supporting Information). [d] Reactions were conducted with a catalytic amount of (*R*)-TolBINAP·AgOTf, 1.0 equiv of nitrosobenzene, and 1.0 equiv of trimethyltin enolate in THF at −78 °C for 2 h.

Turning now to the hydroxyamination issue, due to relatively high *N*-selectivity in the reaction catalyzed by the 10 mol % of AgOTf and (*R*)-BINAP system in THF (*O*-/*N*- = 8:92, 54% ee of *N*-adduct), tributyltin enolate of cycloheptanone was chosen for evaluation of these complexes in the *N*-selective pathway.[9] Complex **A** resulted in complete *N*-selectivity but without any enantioselectivity (*O*-/*N*- = 1:>99, 2% ee of *N*-adduct). The enantioselectivity of *N*-adduct was also very low using complex **B** derived from AgOAc (∼20% ee). A dramatic increase of enantio- and regioselectivities was observed by using complex **C** in THF, to give the *N*-adduct in 87% ee with 96% regioselectivity.

The high enantioselectivity in the use of tin enolate of cycloheptanone associated with the use of complex **C** prompted us to select catalyst **C** for the development of α-hydroxyamino ketone

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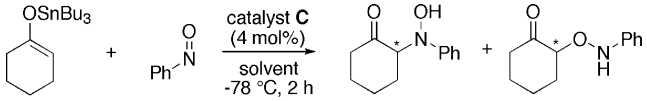
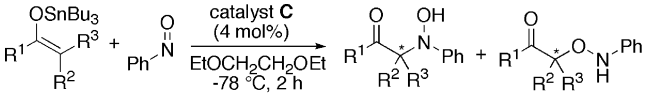
Table 2. Solvent Effect in *N*-Nitroso Aldol Synthesis[a]

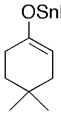


entry	solvent	yield, %[b]	*N*-/*O*-	ee of *N*-adduct, %[c]
1	THF	94	5/95	9
2	DMF	90	94/6	5
3	Et_2O	92	73/27	90
4	$MeOCH_2OMe$	97	92/8	59
5	$MeOCH_2CH_2OMe$	93	92/8	40
6	$EtOCH_2CH_2OEt$	94	96/4	>99
7	$MeOCH_2CH_2O^tBu$	92	93/7	87

[a] Reactions were conducted with 4 mol % of complex **C** (X = OTf), 1.0 equiv of nitrosobenzene, and 1.0 equiv of tributyltin enolate in corresponding solvent at −78 °C for 2 h. [b] Isolated yield. [c] Determined by HPLC (Supporting Information).

Table 3. Reaction Scope in *N*-Nitroso Aldol Synthesis[a]



entry	enolate		yield, %[b]	*N*-/*O*-	ee of *N*-adduct, %[c]
1		n = 1	90	97/3	86
2		n = 2	95	96/4	>99
3		n = 3	96	>99/1	97
4			94	>99/1	77
5			97	>99/1	98

[a] Reactions were conducted with 4 mol % of complex **C** (X = OTf), 1.0 equiv of nitrosobenzene, and 1.0 equiv of tributyltin enolate in ethylene glycol diethyl ether at −78 °C for 2 h. [b] Isolated yield. [c] Determined by HPLC (Supporting Information).

synthesis.[10] Variation of the solvent has a pronounced effect on regio- and enantioselectivity, and some of our results are summarized in Table 2. Generally, the complex **C**-catalyzed *N*-nitroso aldol reaction performs well in a number of ether solvents with moderate-to-high enantioselectivities. Excellent levels of enantio- and regioselectivities were observed when the reaction was carried out in ethylene glycol diethyl ether (Table 2, entry 6).

The benefits of complex **C** extend over a wide range of cyclic substrates, and those experiments that probed the scope of tin enolates in ethylene glycol diethyl ether are summarized in Table 3.[11] Extremely high enantioselectivities were observed during the examination, an indication that complex **C** is indeed very effective and that these reactions proceed via a highly organized transition state.

The synthetic transformations described herein provide new insights into the developing area of catalytic enantioselective nitroso aldol synthesis and new methodology for the construction of a variety of chiral building blocks. Further, the new method of selective generation of three different silver−BINAP complexes opens a new entry into various unknown synthetic reactions. These catalysts are easily generated and provide clear guidance for the design of an even more effective catalyst.

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Supporting Information Available: Experimental procedures, spectral data for all new compounds, and crystallographic data (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) The crystallographic analysis for each species has been described in the Supporting Information.

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(11) Unfortunately, the tin enolate of 3-pentanone could not produce significant enantioselectivity.

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