Asymmetric Catalysis

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Formation of Isoxazolidines by Enantioselective Copper-Catalyzed Annulation of 2-Nitrosopyridine with Allylstannanes**

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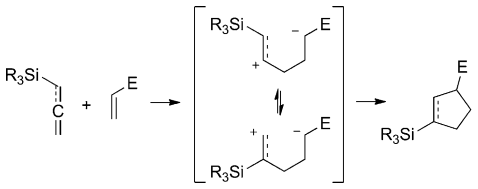
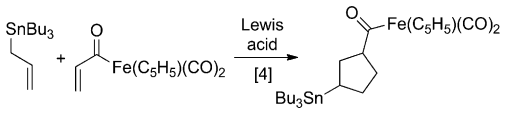
Allenylsilanes[1] and allylsilanes[2] have been successfully used by Danheiser et al. and Knölker et al. as nucleophiles in reactions with activated alkenes using Lewis acids in formal [3+2] cycloadditions for the formation of substituted cyclopentanes. Analogous transformations with heteroolefins C=X (X = O, NR) have also been accomplished to provide the corresponding five-membered heterocycles.[3] These annulations occur through initial C–C bond formation at the γ-C atom of the unsaturated silane with the π acceptor, followed by cationic 1,2-silyl migration and subsequent cyclization [Eq. (1)]. Similar annulations with more-reactive allylstannanes are very rare. To our knowledge, only with α,β-unsaturated acyl iron complexes as acceptors have such formal [3+2] cycloadditions been observed [Eq. (2)].[4]



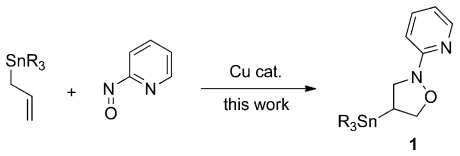
(1)



(2)

Herein we describe unprecedented highly stereoselective annulations of allylstannanes with 2-nitrosopyridine for the preparation of 4-stannyl-substituted isoxazolidines **1** [Eq. (3)].

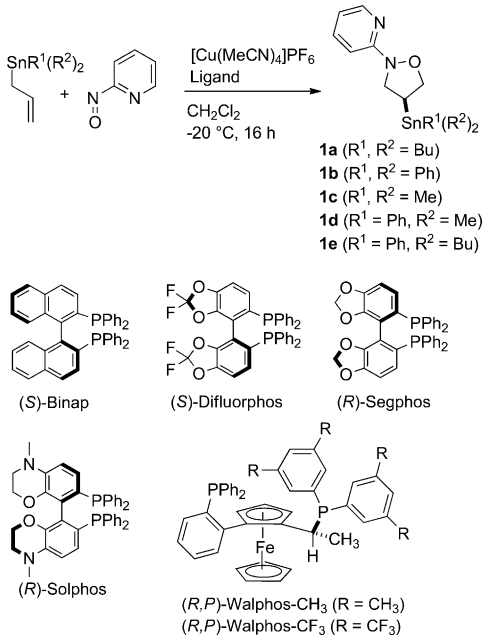
Nitrosopyridines have been used successfully by Yamamoto[5] and us[6] as dienophiles in stereoselective Cu-catalyzed nitroso-Diels–Alder reactions. More recently, we showed that cycloadditions of 2-nitrosopyridine with various ketenes can be catalyzed by Cu^{I} salts to give 1,2-oxazetidin-3-ones with high enantioselectivities.[7] Based on these successful investigations we decided to study other π systems in the reaction with 2-nitrosopyridine. Initial experiments were conducted with allyltrimethylsilane. Various Lewis acids were tested; however, the addition reaction did not occur under the applied conditions. The starting materials were recovered unchanged.



(3)

We therefore switched to the more nucleophilic allylstannanes.[8] Pleasingly, reaction of allyltributyltin with 2-nitrosopyridine in CH_2Cl_2 using $[Cu(MeCN)_4]PF_6$ as the catalyst (10 mol%) and (*S*)-Binap[9a] as the ligand (10 mol%) for 16 h at −20 °C provided **1a** in 31% yield with encouraging selectivity (66% *ee*; Scheme 1, Table 1, entry 1). Interestingly, the possible allylation product (allyl transfer to the nitroso compound) was not identified. The reaction was clean but stopped at low conversion.

Both the yield and the selectivity were increased when the ligands Segphos,[9b] Solphos,[9c] and Difluorphos[9d] were used (Table 1, entries 2–4). The Walphos-CH_3 ligand[9e] delivered the highest yield (77%; Table 1, entry 5). The selectivity was



Scheme 1. Model reaction and ligands tested.

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Table 1: Optimization studies.

Entry	Ligand	Cat. [mol%]	Prod.	Yield [%][a]	*ee* [%][b]
1	(*S*)-Binap	10	**1a**	31	66[c]
2	(*R*)-Segphos	10	**1a**	35	77
3	(*R*)-Solphos	10	**1a**	43	61
4	(*S*)-Difluorphos	10	**1a**	52	86[c]
5	(*R*,*P*)-Walphos-CH_3	10	**1a**	77	74
6	(*R*,*P*)-Walphos-CF_3	10	**1a**	77	96
7	(*R*,*P*)-Walphos-CF_3	5	**1a**	73	96
8	(*R*,*P*)-Walphos-CF_3	2	**1a**	58	96
9	(*R*,*P*)-Walphos-CF_3	10[d]	**1a**	–	–
10	–	–	**1a**	–	–
11[e]	(*R*,*P*)-Walphos-CF_3	10	**1a**	< 5	–
12	(*R*,*P*)-Walphos-CF_3	10	**1b**	47	96 (99)[f]
13	(*R*,*P*)-Walphos-CF_3	5	**1b**	45	96 (99)[f]
14	(*R*,*P*)-Walphos-CF_3	10	**1c**	76	98
15	(*R*,*P*)-Walphos-CF_3	5	**1c**	71	98
16	(*R*,*P*)-Walphos-CF_3	10	**1d**	63	97
17	(*R*,*P*)-Walphos-CF_3	10	**1e**	62	96

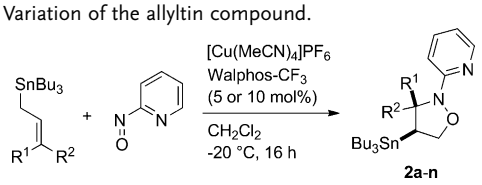
[a] Yield of isolated product (reactions conducted at 0.14 mmol scale). [b] Determined by HPLC on a chiral stationary phase (see the Supporting Information). [c] *R* enantiomer formed. [d] With ligand in the absence of $[Cu(MeCN)_4]PF_6$. [e] In THF as a solvent. [f] After crystallization.

further increased to 96% *ee* without affecting the yield by switching to the CF_3 congener (Table 1, entry 6). Reducing the catalyst loading to 5 and 2 mol% led to slightly lower yields while the excellent selectivity was maintained (Table 1, entries 7 and 8, respectively). The ligand alone did not catalyze the process (Table 1, entry 9) and a background reaction did not occur (Table 1, entry 10). In THF only a trace amount (< 5%) of the product was formed (Table 1, entry 11). With triphenylallyltin, isoxazolidine **1b** was formed in significantly lower yield but also excellent selectivity (Table 1, entries 12 and 13). Enantiomerically pure material was isolated after a single crystallization. Based on the X-ray structure of **1b** the absolute configuration (*S* enantiomer) was unambiguously determined (Figure 1).[10] Absolute configuration of other products was assigned in analogy. The highest selectivity (98% *ee*) was achieved with allyltrimethyltin (Table 1, entries 14 and 15).

It is evident from these results that the size of the "non-allylic" substituents at Sn strongly influences reactivity: the phenyl-substituted tin derivative gave the lowest yield, whereas the trimethyl-substituted systems provided the highest yield. Along this line, allyldialkylphenyltin derivatives provided intermediate yields (**1d** and **1e**; Table 1, entries 16 and 17). Switching from methyl to butyl substituents did not influence reactivity to a large extent (compare Table 1, entries 6 and 14, and 16 and 17).

Under optimized conditions we reacted various isomerically pure 2-alkenyltributylstannanes with 2-nitrosopyridine using catalyst loadings of 10 and 5 mol% (Table 2). *Z*-2-

Table 2: Variation of the allyltin compound.



Entry	R^1	R^2	Prod.	Yield [%][a,b]	d.r.	*ee* [%][c]
1	Me	H	**2a**	> 99 (97)	> 99:1	> 99
2	Et	H	**2b**	83 (81)	> 99:1	99
3	*n*-Pr	H	**2c**	80 (78)	> 99:1	98
4	*n*-Hex	H	**2d**	84 (82)	> 99:1	> 99
5	$CH_2CH_2CH(CH_3)_2$	H	**2e**	81 (80)	> 99:1	> 99
6	*i*Pr	H	**2f**	81 (80)	> 99:1	> 99
7	*t*Bu	H	**2g**	71 (63)	> 99:1	> 99
8	CH_2OCH_2Ph	H	**2h**	93 (93)	> 99:1	98
9	OMe	H	**2i**	94 (93)	> 99:1	96
10	H	Me	**2j**	72 (72)	2:1	98[d]
11	H	Et	**2k**	45 (44)	> 99:1	64
12	H	Ph	**2l**	29 (26)	> 99:1	45
13	Me	Me	**2m**	63 (61)	–	96
14	$CH_2CH_2CH(CH_3)_2$	Me	**2n**	46 (44)	> 99:1	> 99

[a] Yield of isolated product (reactions conducted at 0.14 mmol scale). [b] Yield with 10 mol% cat. loading and (in brackets) with 5 mol% cat. loading. [c] Determined by HPLC on a chiral stationary phase (see the Supporting Information). [d] Minor isomer **2a** was formed with > 99% *ee*.

Butenyltributyltin was the most reactive substrate in these studies and the formal [3+2] cycloaddition delivered adduct **2a** in a quantitative yield with perfect selectivity (Table 2, entry 1). At 5 mol% catalyst loading the yield was still very high (97%). For this stannane we conducted the reaction using 0.5 mol% of the catalyst (run on a 1 mmol scale) and obtained **2a** as a single isomer in 96% yield. The *cis* relative configuration and the regiochemistry were unambiguously assigned by ^{1}H NMR spectroscopy (see the Supporting Information). Increasing the size of the R^1 substituent in the *cis*-2-alkenyltributylstannanes led to slightly lower but still very good yields, perfect diastereoselectivties, and excellent enantioselectivities (Table 2, entries 2–8). Also stannylated enol ethers proved to be good substrates, as shown by the preparation of **2i** (Table 2, entry 9).

To investigate the stereospecificity of the annulation we tested *E*-2-butenyltributyltin and found that reaction was sluggish compared to the transformation with the *cis* isomer. Surprisingly, reaction was not stereospecific and **2j** was isolated along with the minor isomer **2a** (ratio 2:1). Enantio-

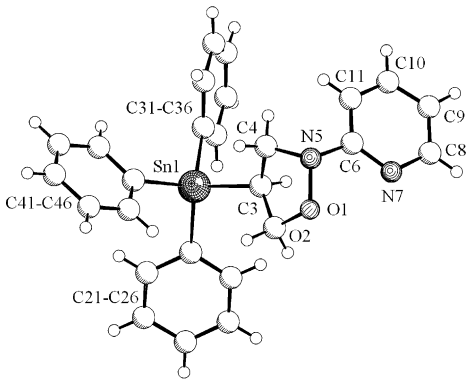
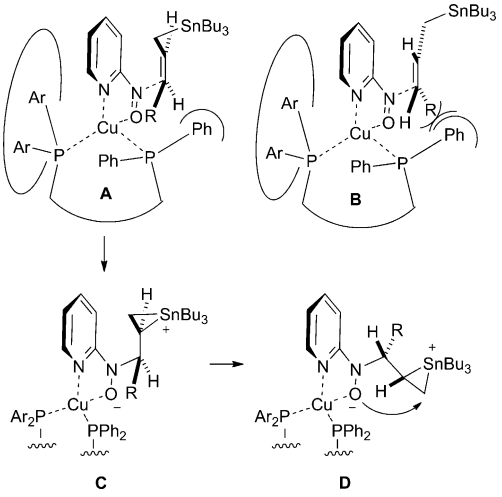


Figure 1. X-ray crystal structure of **1b**.

selectivity was high for both isomers (Table 2, entry 10) and the absolute stereochemistry adjacent to the N atom was opposite in **2a** and **2j**. This was experimentally proven by transforming these diastereoisomeric compounds into enantiomeric allyl-1-methylamine derivatives (see the Supporting Information). As expected, the absolute stereochemistry next to the Sn atom did not alter upon switching from the *cis*-allylstannane to its *trans* derivative. Likely isomerization occurred during reaction.[11]

The larger ethyl- and phenyl-substituted *trans* isomers reacted with excellent stereospecificity (d.r. > 99:1) but moderate enantioselectivity and lower yields (Table 2, entries 11 and 12).[12] Importantly, our method allowed formation of quaternary C centers with excellent selectivity (Table 2, entries 13 and 14). For the unsymmetrically substituted stannane leading to **2n**, both the diastereoselectivity and the enantioselectivity were excellent (Table 2, entry 14).

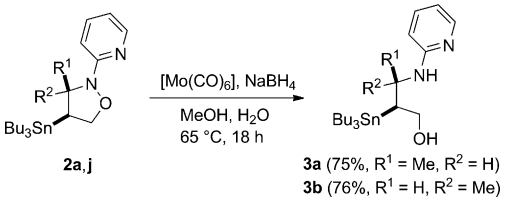
We propose the following model to explain the stereochemical outcome of the highly selective reaction with *cis*-allylstannanes (Scheme 2). Based on the rigid ground-state



Scheme 2. Model to explain the stereochemical outcome.

conformation of the nitroso Cu-Walphos-CF_3 complex recently calculated by us,[6c] addition of the nucleophile should occur to the *Re* face of the nitroso compound. Since isomerization of *cis*-allyltin derivatives to their *trans* isomers was not observed during reaction, we currently exclude formation of allyl-Cu intermediates. We assume an *anti* orientation of the two π systems in the transition state.[13] **A** is favored over **B** because of the unfavorable interaction of the R substituent with a phenyl group of the ligand, as indicated in Scheme 2. This phenyl group was also found to be important for the stereochemical control in enantioselective nitroso-Diels–Alder reactions.[6c] Addition via **A** leads to **C** which undergoes C–C bond rotation to give **D** which eventually cyclizes to provide the observed products.

As a first follow-up reaction, we showed that N–O bond cleavage in the isoxazolidines **2a** and **2j** could be readily achieved upon treatment with $[Mo(CO)_6]/NaBH_4$.[5a,6,14] The corresponding N-protected amino alcohols **3a** and **3b** were isolated in 75% and 76% yield, respectively (Scheme 3).



Scheme 3. Reductive N–O bond cleavage.

In conclusion we have reported first examples of highly enantioselective formal [3+2] cycloadditions of allyltin derivatives with 2-nitrosopyridine to give substituted isoxazolidines. Our process represents a new approach to isoxazolidines which are important heterocycles. The products obtained are interesting compounds for further synthetic transformations. The reactions occur under mild conditions and the starting materials are readily prepared.

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[10] CCDC 837081 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] There was no indication of isomerization of the thermodynamically more stable *E*-2-butenyltributyltin to its *Z* isomer in the absence of 2-nitrosopyridine under the reaction conditions (^{1}H NMR analysis). However, since the *cis* isomer is very reactive, only little isomerization would explain the reaction outcome.

[12] It seems that the pyridyl group might stabilize the intermediately formed cationic stannacyclopropane (see structure **C** in Scheme 2). In the reaction of the *trans*-allyltributylstannanes this interaction forces the substituent R to be placed next to the shielding phenyl group. This is likely the reason why a drop in selectivity was observed with *trans*-allyltributylstannanes with R substituents larger than methyl.

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