Communication

A Chiral Phenanthroline Ligand with a Hydrogen Bonding Site: Application to the Enantioselective Amination of Methylene Groups

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A Chiral Phenanthroline Ligand with a Hydrogen Bonding Site: Application to the Enantioselective Amination of Methylene Groups

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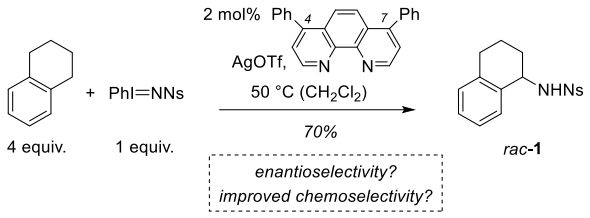
Supporting Information Placeholder

ABSTRACT: A silver-catalyzed amination is reported which occurs at the aliphatic C_3-substituent of various quinolones and pyridones. The C-H amination reaction proceeded with high site- and enantioselectivity (14 examples, 83-97% *ee*). Key to its success is the use of a chiral phenanthroline ligand that is attached via an ethynyl linker to the 8-position of octahydro-1*H*-4,7-methanoisoindol-1-one. $AgPF_6$ (10 mol%) served as the silver source, PhINNs as the nitrene precursor and 1,10-phenanthroline as the coligand. The reaction outcome can be understood by assuming a nitrene C-H insertion within a hydrogen-bonded silver complex in which a single C-H bond is exposed to the catalytic reaction center.

The ubiquitous presence of amino-substituted alkyl moieties in biologically active compounds has stimulated extensive synthetic work on the stereoselective introduction of an amino group.[1] Traditional approaches rely on nucleophilic substitution reactions which require a pre-functionalization at the respective sp³-carbon atom. A more straightforward approach aims at the direct insertion of a nitrene or nitrene precursor into a C-H bond.[2] Major challenges to be met for this strategy to be successful include the control of several selectivity parameters, such as chemoselectivity, site-selectivity and most notably enantioselectivity. Particularly, the intermolecular enantioselective amination at prostereogenic methylene groups poses a formidable challenge and requires new concepts for the construction of suitable catalysts.[3] Previous studies on chiral metal complexes that enable an enantioselective *inter*molecular sp³-C-H amination reaction can be grouped by the choice of ligands. A chiral modification of rhodium complexes has been frequently attempted with chiral carboxylates[4] and has led to remarkably efficient catalysts, as shown by the groups of Davies[5] and Dauban.[6] Matsunaga and co-workers have successfully employed chiral carboxylates in combination with rhodium and cobalt complexes.[7] The Che group demonstrated that chiral porphyrins[8] are suitable tetradentate ligands if the catalytically active center is manganese or ruthenium.[9] Studies by Katsuki and co-workers have established that chiral salens represent another class of tetradentate ligands which can be combined with the same metals to achieve an enantioselective intermolecular amination.[10] Clark and Roche have exploited with considerable success chiral bisoxazolines for copper-catalyzed amination reactions.[11]

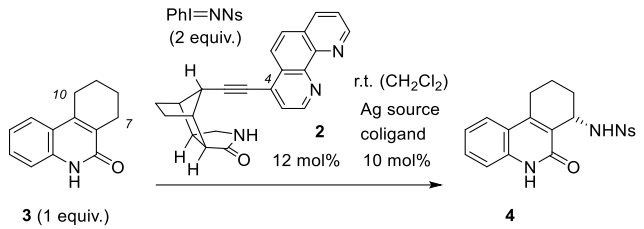
Scheme 1. First Report on an Ag-Catalyzed Intermolecular Amination Reaction by He and co-workers[12]



When searching for new classes of catalysts and chiral ligands to be used in enantioselective amination reactions, we came across the silver-catalyzed amination reaction originally reported by He and co-workers (Scheme 1).[12] Although the fact that the nitrene precursor *N*-(p-nitrophenylsulfonyl)imino]-phenyl iodinane (PhI=NNs) was used as the limiting reagent was not optimal, the low catalyst loading and the conceptually novel approach were appealing to us. In more recent years, the chemistry of silver-catalyzed nitrene transfer has been more extensively studied,[13] most notably by the groups of Schomaker[14] and Pérez.[15] Although an enantioselective intramolecular aziridination has been achieved with a chiral silver complex,[16] intermolecular amination reactions have to the best of our knowledge remained elusive.

We envisioned that chiral phenanthroline ligands could be created by covalently attaching the phenanthroline core to a chiral octahydro-1*H*-4,7-methanoisoindol-1-onyl skeleton[17,18] which exhibits a hydrogen bonding site for substrate coordination. Starting from 3-, 4-, and 5-bromophenanthroline, the respective Sonogashira cross-coupling reactions led to the desired ligands (see the SI for further details). Based on the analysis of molecular models, preliminary experiments were performed with ligand **2** (Table 1) in combination with silver triflate (10 mol%) as the silver source and PhI=NNs as the nitrene precursor (2 equiv.). The chosen substrate was 7,8,9,10-tetrahydro-6(5*H*)-phenanthridinone (**3**) which displays a lactam binding site and four non-identical methylene groups within the cyclohexene ring. At ambient temperature a slow but notable conversion was observed from which a single regioisomeric product **4** was isolated with a significant enantiomeric excess (*ee*) of 65% (entry 1).

Table 1. Optimization of the Catalytic Enantioselective Amination of Substrate 3 by Variation of the Silver Salt and the Coligand (30 μmol scale)

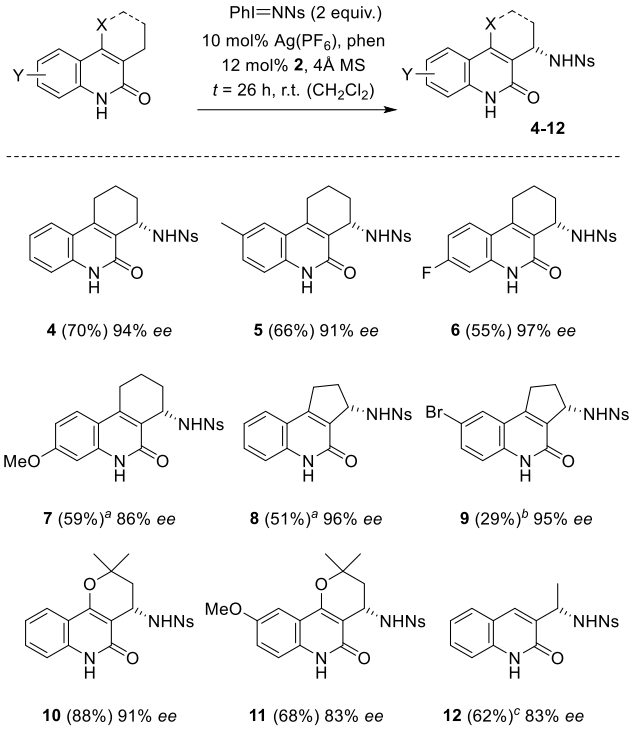


entry[a]	Ag source	coligand	yield (%)[b]	*ee* (%)[c]
1	AgOTf	—	34	65
2	AgOTf	4,7-(Ph_2)-phen	60	78
3	AgOTf	4,7-(Me_2)-phen	71	80
4	AgOTf	4,7-(MeO_2)-phen	50	82
5	AgOTf	3,4,7,8-(Me_4)-phen	48	73
6	AgOTf	2,9-(Me_2)-phen	27	38
7	AgOTf	phen	69	81
8	Ag(BF_4)	phen	70	85
9	Ag(SbF_6)	phen	77	88
10	Ag(PF_6)	phen	74	94
11[d]	Ag(PF_6)	phen	70	84
12[e]	Ag(PF_6)	phen	<10	—

[a] The reaction mixture was stirred for 26 hours (c = 10 mM) in the presence of 4Å molecular sieves (4Å MS); low yields indicate low conversion (see SI). [b] Yields were determined by ^{1}H-NMR spectroscopy using dimethyl fumarate as the internal standard. [c] The enantiomeric excess was calculated from the ratio of enantiomers (**4**/*ent*-**4**) as determined by chiral HPLC analysis. [d] The 5-substituted isomer of **2** was employed. [e] The 3-substituted isomer of **2** was employed.

Since it had been shown in mechanistic studies by Berry and Schomaker that bis(phenathroline) complexes are involved in nitrene transfer reactions[14d] an achiral phenanthroline coligand was added (entries 2-7) to favor formation of a heteroleptic vs. a homoleptic silver complex. Indeed, several coligands facilitated an accelerated and more selective reactions with the unsubstituted 1,10-phenanthroline (phen) displaying together with 4,7-(Me_2)-phen the best results. Optimization was continued by varying the counterion of the silver complex and an increase of enantioselectivity was recorded for OTf < BF_4 < SbF_6 < PF_6 (entries 7-10). The best conditions led to product **4** in a yield of 74% and with 94% *ee*. The superior performance of ligand **2** as compared to its constitutional isomers (3- and 5-phenanthroline substitution) was confirmed by performing the reaction under optimized conditions but with the latter ligands (entries 11, 12). The 5-substituted isomer was catalytically active but resulted in a lower enantioselectivity (entry 11) while the 3-substituted isomer turned out to be not competent to promote the reaction (entry 12). The site-selectivity of the amination showed a clear preference for an attack at position C7 of the phenanthridinone substrate. The electronically similar position C10 remained untouched nor was any other of the methylene groups involved in the amination reaction.

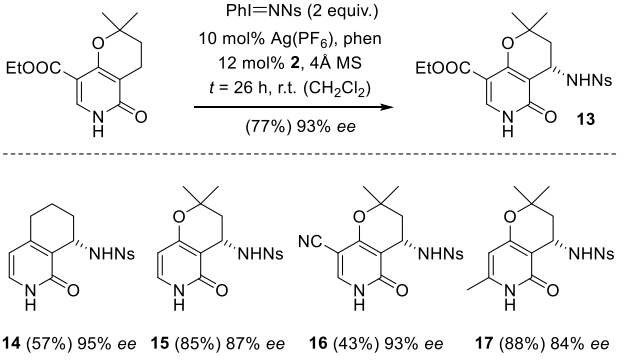
Table 2. Enantioselective Ag-Catalyzed Amination of Various 2-Quinolone Substrates Employing Ligand 2 as the Source of Chirality (60 μmol scale)



[a] 88% conversion. [b] 78% conversion. [c] 86% conversion.

When performing the reaction on preparative scale under optimized conditions (Table 2), we could isolate product **4** with the same enantioselectivity (94% *ee*) and a similar yield as in the preliminary experiments. The absolute configuration at the stereogenic center (*S*) was determined by single crystal X-ray crystallography (see the SI). The functional group tolerance of the reaction was established for methyl (product **5**), fluoro (product **6**), and methoxy (product **7**). A modification of the annulated ring at the quinolone core was tolerated by the chiral silver catalyst and conversion to aminated products **8**, **9**, **10**, and **11** was achieved with high enantioselectivity. The reaction with 6-bromo substituted quinolone was sluggish and did not go to completion. Even an acyclic ethyl group at position C3 of the quinolone was processed with a high preference for amination at one of the two enantiotopic methylene C-H bonds (product **12**).

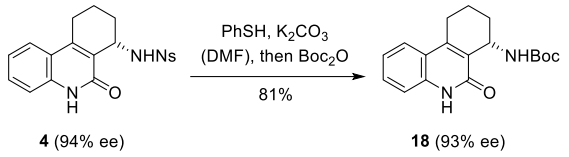
Table 3. Enantioselective Ag-Catalyzed Amination of Various 2-Pyridone Substrates (60 μmol scale)



An extension of possible substrates was attempted by employing annulated pyridones as substrates (Table 3). To our delight, it was found that products **13**-**17** were consistently generated in high yield and with excellent enantiomeric excess. The enormous impact of the hydrogen bonding event was not only corroborated by the high site- and enantioselectivity of the amination protocol but also by the significantly increased activity of the catalyst as compared to any achiral silver complex. In several cases, racemic material which was required for HPLC comparison was not accessible by a silver-catalyzed amination reaction with achiral phenanthroline ligands. Instead, we had to use racemic ligand *rac*-**2** to get our hands on racemic products (see the SI for further details).

A major benefit of the nosyl (Ns) compared to other sulfonyl-based protecting groups is their facile cleavage from a given nitrogen atom.[19] We demonstrated for product **4** that the cleavage can be readily performed with thiophenol and that an *in situ* protection of the free amine with the most common amine protecting group *tert*-butoxycarbonyl (Boc) was possible (product **18**, Scheme 2). The method is thus suited to introduce amino groups enantioselectively in heterocyclic skeletons of biological relevance.[20]

Scheme 2. Facile Cleavage of the Nosyl Protecting Group and *in situ* Boc Protection



Some preliminary mechanistic experiments were performed to elucidate the origin of the selectivity. When racemic product *rac*-**4** was submitted to the optimized amination conditions (Table 2), there was a 60% conversion, presumably due to consecutive oxidation or decomposition. Unreacted substrate was isolated in 40% yield in a low enantiopurity of 33% *ee*. An *s* factor of 2.1 was calculated from this data (Figure 1) which in turn confirms that the high enantioselectivity of the amination reaction was not due to a kinetic resolution.

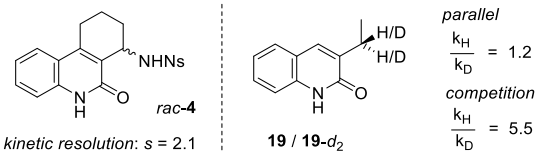


Figure 1. Under the standard reaction conditions, substrate **4** shows almost no kinetic resolution indicated by a small $s = k_S/k_R$; kinetic isotope effect (k_H/k_D) determined from parallel and competition reactions on non- and doubly deuterated 3-ethylquinolin-2-one **19** and **19**-d_2.

The nature of the C-N bond forming step was interrogated by kinetic isotope effect (KIE) measurements.[21] To this end, 3-ethylquinolin-2-one (**19**) and its double deuterated analogue **19**-d_2 were subjected to the amination reaction. The reaction led to product **12** in the former case and to product **12**-d_1 in the latter case. In parallel experiments in which the ratio of the individual rates k_H/k_D was determined after ca. 10% conversion a low KIE of only 1.2 was observed. In a competition experiment, in which equimolar amounts of **19** and **19**-d_2 were subjected to the reaction condition in a single flask, the KIE was higher. The relative ratio of **12** and **12**-d_1 was determined by ^{1}H NMR spectroscopy after ca. 30% conversion and a primary KIE of 5.5 was calculated. Albeit preliminary, the results suggest the C-H insertion to be not rate-determining. In the selectivity-determining step, a significant differentiation by the catalyst seems to occur, however. Based on the known coordination behavior of silver bis(phenanthroline) complexes[14d] it is suggested that the silver salt and the two ligands form heteroleptic complex **20** with a tetrahedral coordination sphere around the metal and a free site for hydrogen bonding by the substrate (Figure 2). Upon rate-determining delivery of the nitrene fragment from PhI=NNs to the silver atom the coordination sphere is expanded to a distorted trigonal bipyramid[14c] and the amination occurs site- and enantioselectively because only one of the hydrogen atom is properly displayed to the active center as indicated by structure **21**. The observed primary KIE of 5.5 is congruent with values obtained for some intermolecular rhodium- and ruthenium-catalyzed amination reactions (KIE = 4.5-4.8)[22] and suggests a transition state in which the C-H bond is significantly elongated. It has been proposed for a related intramolecular silver-catalyzed amination (KIE = 3.4) that the reaction proceeds by attack of a triplet nitrene species which undergoes intersystem crossing prior to the formation of any intermediates.[14c,15b] A similar scenario is conceivable also for the reaction within complex **21**.

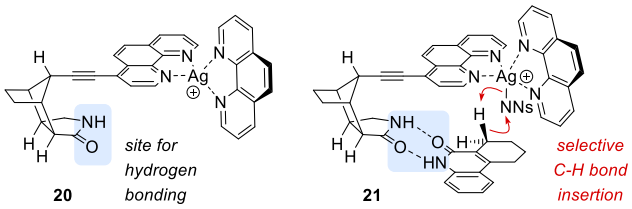


Figure 2. Proposed structure **20** of the 1:1:1 complex of $Ag(PF_6)$, ligand **2** and 1,10-phenanthroline (phen): Upon transfer of the nitrene fragment from PhI=NNs to the catalyst the reaction occurs with high enantioselectivity within the hydrogen bonded complex **21**.

In summary, the site- and enantioselective amination of aliphatic methylene groups in pyridones and quinolones has been achieved by silver catalysis. The chiral ligand **2** employed for asymmetric induction bears a hydrogen bonding site which displays in a highly predictable fashion a single C(sp^3)-H bond to the reactive center. Only methylene groups attached to the C_3 carbon atom of the heterocycles are attacked. Studies are underway to explore the reaction course in more detail and to find other transition metal-catalyzed reactions in which the chiral phenanthroline ligand **2** exerts a similar directing effect.

Supporting Information

Experimental procedures, analytical data for all new compounds, proof of constitution and configuration (crystal data of product **4**), kinetic resolution and KIE experiments, NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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