Enantioselective Silver and Amine Co-catalyzed Desymmetrizing Cycloisomerization of Alkyne-linked Cyclohexanones

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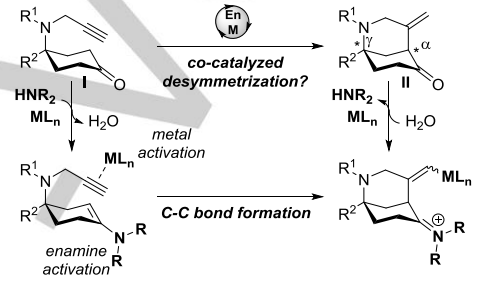
Abstract: A silver(I) and amine co-catalyzed desymmetrization of 4-propargylamino cyclohexanones for the direct enantioselective synthesis of 2-azabicyclo[3.3.1]nonanes is described. Exploiting reactivity arising from dual activation of the pendant terminal alkyne by silver(I) and the ketone moiety through transient enamine formation, this synthetically relevant transformation is easy to perform, efficient and broad in scope. High enantioselectivity (up to 96% ee) was achieved by exploiting a significant matching effect between the chirality of a cinchona alkaloid-derived aminophosphine ligand for the silver(I) salt and the 2-bis(aryl)methylpyrrolidine catalyst which was rationalized by DFT calculations. This allowed for the preparation of both enantiomers of the bicyclic product with near-identical stereocontrol.

In recent years, the demand for ever-increasing efficiency in the synthesis of structurally complex and stereochemically defined molecular constructs has spawned numerous lines of research in the field of enantioselective catalysis. One particular strand, where multiple catalytically competent and compatible species are employed simultaneously to achieve reactivity unattainable by a single catalytic entity alone, has been particularly successful.[1] In this regard, the co-operative combination of aminocatalysis and transition metal catalysis has been demonstrated to be a powerful and versatile catalytic strategy for the enantioselective construction of C-C bonds,[2] which has found applications in both library synthesis and natural product synthesis alike.[3]

The use of terminal alkynes as electrophilic partners for carbonyl compounds in co-operative metal and amine co-catalysis was first reported independently by our group and the Kirsch group in 2008.[4] Racemic cyclopentane derivatives were prepared by a copper-catalyzed cascade reaction between α,β-unsaturated ketones and propargylmalonates in the former case, and by a gold-catalyzed intramolecular cyclization of 1,7-ynals in the latter. Enantioselective variants of both 5-endo-dig cyclizations with aldehydes as starting materials were later disclosed.[5],[6]

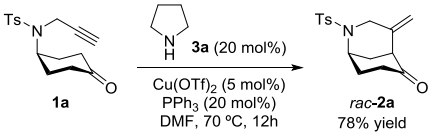
In a continuation of our research program into expanding the synthetic possibilities of co-operative co-catalytic transformations we took inspiration from nature. A wide variety of natural products and biologically relevant molecules contain the morphan core (2-azabicylo[3.3.1]nonane) in their structures, including the *daphniphyllum* and *strychnos* alkaloid families,[7] and accordingly the development of new, efficient and stereoselective methods for the construction of this motif is highly desirable. In this context, an organocatalyzed intramolecular Michael addition to α,β-unsaturated esters[8a] and an enantioselective arylation of cyclohexanones have been reported.[8b]



Scheme 1. Metal and amine co-catalyzed desymmetrization concept.

We envisaged that an enantioselective desymmetrizing[9] cycloisomerization of prochiral scaffold **I** (Scheme 1) to afford the 6,6-bicyclic morphan skeleton **II** could possibly be realized using a co-operative metal and amine co-catalyst system. Under appropriate reaction conditions, the aminocatalyst would generate *in situ* a nucleophilic enamine intermediate, which would be poised to react intramolecularly with the pendant alkyne when suitably activated by a 'soft' late transition metal ion, such as a copper or silver species.[10] Such an enantioselective transformation to a strained 6,6-bicyclic morphan core has not previously been described despite its potential use in synthesis and herein we wish to disclose our findings.

Our hypothesis was validated following a series of experiments with substrate **1a**, which was accessible on scale from simple commercial starting materials. Treatment of **1a** with catalytic amounts of pyrrolidine, $Cu(OTf)_2$ and triphenylphosphine [as a reducing agent and ligand for copper] in DMF at 70 °C for 12 hours provided the racemic morphan product **2a** in good yield (Scheme 2). Control experiments omitting any one of these three components produced no or insignificant amounts of **2a** (see SI for details). Additionally, *N*-methylpyrrolidine was found to be catalytically incompetent in the reaction. Taken together these preliminary studies suggested that both enamine activation of the ketone group and transition metal activation of the alkyne were required for a productive carbocyclization.



Scheme 2. Proof of concept.

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Consequently, we continued our investigations by evaluating the enantioselective version of this reaction. Considering the literature precedents[4-6] and the preliminary studies described above, an obvious approach was to investigate the combination of a soft transition metal species with chiral amines and/or chiral phosphines.

Initial experiments demonstrated that a combination of chiral 2-bis(aryl)methylpyrrolidines (**3d-e**) and cinchonidine-derived aminophosphine (**4a**)[11] in conjunction with a copper salt made an excellent starting point for a co-catalytic system (Table 1). Primary amines or proline (**3c**) provided very low enantiocontrol and variable reactivity (entry 2 and SI for full details). Although the typically successful diarylprolinol silyl ether catalyst **3b** was inefficient in this transformation (entry 1),[12] a sterically less demanding desilyloxy derivative[13] (**3d**) was found to be very promising, especially when combined with the readily available cinchonidine-derived aminophosphine **4a** (entries 3-4). Whereas copper salts provided enhanced reactivity, silver acetate induced higher enantiocontrol (entries 4-5) and consequently the remainder of our studies focused on silver salts as the metal co-catalyst. Modifications to the catalyst structure **3d** led to the identification of the 3,5-bis(trifluoromethyl)phenyl-derived pyrrolidine (**3e**) as the most enantioselective catalyst, which afforded **2a** in 92% ee (entry 6).

The poor catalytic turnover was greatly improved by the use of inexpensive 2,4-dinitrophenol (DNP) as an acidic additive (entry 7).[14,15] Furthermore, protic solvents had previously been reported to accelerate some reactions[14] and indeed 2-propanol was found to be the optimal solvent for this transformation (entry 8). It is likely that the protic medium assists the protodemetallation step[16] and/or facilitates enamine formation.[17] After fine tuning of the silver source and the temperature (see SI for details), we found that the combination of chiral pyrrolidine **3e**, $AgNTf_2$, aminophosphine **4a** and 2,4-dinitrophenol smoothly promoted the targeted reaction in 2-propanol at 60 ºC, and product **2a** was isolated quantitatively with 95% ee (entry 9). The related ligand **4b**, possessing an *N*-Me group on the amide, provided good enantioselectivity, but a very low yield (entry 10). Control experiments showed that all components were either essential or important for the excellent reactivity and enantioselectivity.

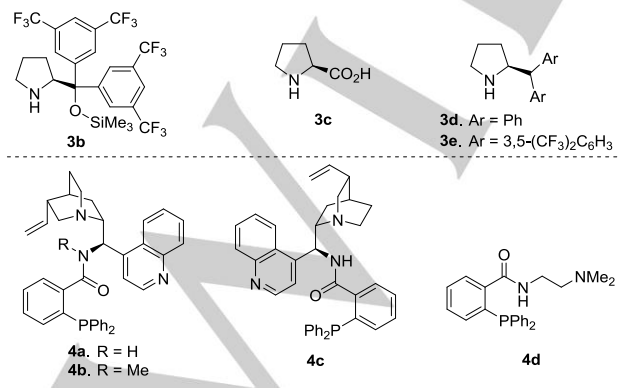
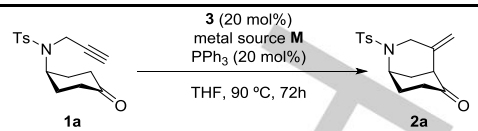


Figure 1. Chiral amines and aminophosphine ligands.

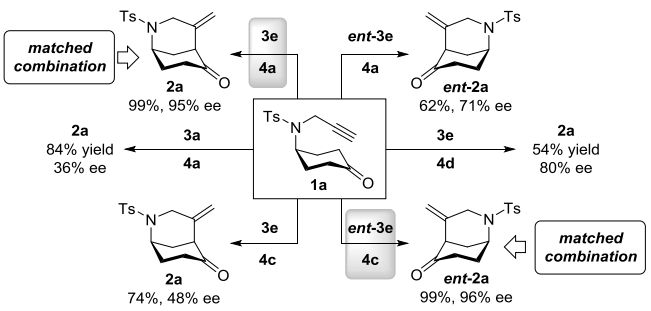
Table 1. Development of an enantioselective variant.



Entry[a]	3	M	ligand	%yield[b]	%ee[c]
1	**3b**	$Cu(OTf)_2$	PPh_3	20	15
2	**3c**	$Cu(OTf)_2$	PPh_3	82	0
3	**3d**	$Cu(OTf)_2$	PPh_3	74	52
4	**3d**	$Cu(OTf)_2$	**4a**	70	71
5	**3d**	AgOAc	**4a**	20	83
6	**3e**	AgOAc	**4a**	11	92
7[d]	**3e**	AgOAc	**4a**	82	91
8[d,e]	**3e**	AgOAc	**4a**	99	90
9[d,e,f]	**3e**	$AgNTf_2$	**4a**	99	95
10[d,e,f]	**3e**	$AgNTf_2$	**4b**	15	90

[a] Conditions: **1a** (0.1 mmol), **3** (20 mol%), ligand (20 mol%), $Cu(OTf)_2$ (5 mol%) or AgOAc (10 mol%) in THF (0.5 mL) at 90 ºC for 72 h. [b] Isolated yield. [c] ee determined by chiral HPLC. [d] 2,4-Dinitrophenol (20 mol%) was used. [e] *i*-PrOH instead of THF. [f] At 60 ºC.

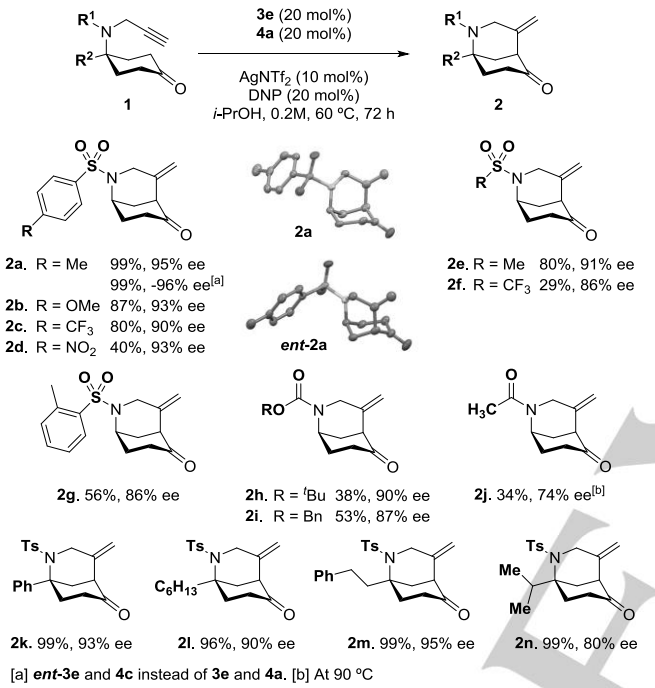
As initially proposed, a significant match/mismatch effect was in operation between both chiral components of the catalytic system (Scheme 3). The matched combination of *R*-configured pyrrolidine ***ent*-3e** with cinchonine-derived aminophosphine **4c** afforded the enantiomeric morphan product ***ent*-2a** with the same high efficiency and high enantioselectivity as **3e** and **4a** (Scheme 3, compare top-left and bottom-right).[18] On the contrary, the use of the mismatched pairs **3e**/**4c** or ***ent*-3e**/**4a** (Scheme 3, compare bottom-left, top-right) provided the product with a diminished enantioselectivity. The use of achiral pyrrolidine **3a** and cinchonidine-derived aminophosphine **4a** gave rise to minimal enantiocontrol in the reaction (36% ee), whereas the use of achiral ligand **4d** and chiral pyrrolidine **3e** afforded product **2a** with a substantial 80% ee. These results demonstrate that the pyrrolidine is exerting the dominant stereocontrolling force in the reaction.



Scheme 3. Match/mismatch effects. (Conditions as for Table 1, entry 9).

With a reliable and optimal procedure in hand, we then assessed the scope of this enantioselective morphan-generating desymmetrization reaction (Scheme 4). Electron-rich and electron-poor aromatic sulfonamides (**1b-c**), as well as an aliphatic one (**1e**) were good substrates affording products in

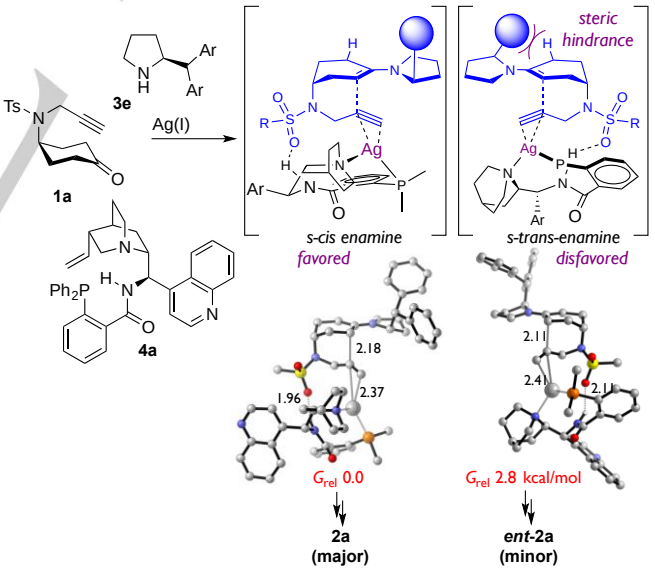
high yield and enantioselectivity. It was observed that strongly electron-deficient sulfonamides, like 4-nosyl and triflyl derivatives **2d** and **2f**, were obtained with a moderate yield but good enantioselectivity. Carbamates **1h-i** were well-tolerated and the respective products **2h-i** were obtained with good enantiocontrol. Acetamide protected product **2j** was afforded in only moderate yield and with a slightly reduced enantiocontrol. Importantly, additional substituents at the 4-position of the cyclohexanone ring were perfectly tolerated, and a variety of morphan products possessing a quaternary stereocenter (**2k-n**) were prepared in excellent yields with high enantioselectivity.



[a] ***ent*-3e** and **4c** instead of **3e** and **4a**. [b] At 90 ºC

Scheme 4. Scope of the enantioselective desymmetrization reaction. [Conditions: **1** (0.2 mmol), **3e** (20 mol%), **4a** (20 mol%), $AgNTf_2$ (10 mol%) and 2,4-dinitrophenol (20 mol%) in 2-propanol (1.0 mL) at 60 ºC for 72 h. Isolated yield. ee determined by chiral HPLC].

Based on a quinine-derived aminophosphine-silver complex recently characterized by X-ray analysis,[19] we have performed DFT computations of enamine intermediates and competing transition structures (TSs) which account for the stereochemical outcome of the reaction (Scheme 5).[20] The aminophosphine-silver complex is likely formed rapidly by coordination of the quinuclidine nitrogen, the phosphorus atom and the amide nitrogen to the silver center. Condensation of the pyrrolidine catalyst with the carbonyl group of **1a** generates a nucleophilic enamine intermediate poised for C-C bond formation upon alkyne activation. The terminal alkyne of this adduct can be accommodated as a π-ligand by the silver complex. Although the *s-trans* rotamer of aldehyde-derived enamines is clearly favored,[21] the reactive conformation of ketone-derived enamines depends on the functionality at the 2-position of the pyrrolidine ring, as demonstrated in the well-studied reaction between cyclohexanone and nitrostyrene catalyzed by chiral pyrrolidines.[22] For reactions catalyzed by pyrrolidines with a substituent able to establish H-bond interactions with the substrate, *s-trans* enamines have been proposed and calculated,[23] but when the substituent on the catalyst acts simply as a bulky group, the stereochemical outcome is explained through *s-cis* enamines.[24] Significantly, in this type of transformations it has also been observed that, with the same catalyst system, the enantioselectivity is reversed when an aldehyde is used instead of a ketone.[25] With catalyst **3d** an SMD-M06-2X/def2-TZVP//def2-SVP conformational analysis reveals a 3 kcal/mol preference for the *s-cis* enamine geometry in the ground state, in which the sterically demanding diarylmethyl group is positioned preferably above the flat olefinic sp^2 carbon rather than above the bulkier tetrahedral sp^3 carbon by 3 kcal/mol. This preference is maintained in the competing TSs, in which the electrophile must approach from the opposite side to this bulky group. A secondary H-bonding interaction (N-H---O < 2.5Å) between sulfonate and amidic N-H group of the aminophosphorane **4a** or **4d** was found in the computed TSs.[26] For chiral aminophosphine **4a**, the matched TS has a shorter N-H---O interaction to the sulfonate group than in the mismatched case (1.96Å *vs.* 2.11Å) – the greater stability reflected by an increase in $\Delta\Delta G^{\ddagger}$ to 2.8 from 1.2 kcal/mol with achiral **4d**. The low efficiency of ligand **4b**, with an *N*-Me group on the amide, compared to that of **4a** (Table 1, entries 9 and 10) indicates the importance of the free N-H amide. This assembly would be less favored by more electron deficient sulfonamide groups, in line with the lower reactivity observed for substrates **1d** and **1f** (Scheme 4).



Scheme 5. Computed (SMD-M06-2X/def2-TZVPP//def2-SVP) transition structures for C-C formation of major and minor enantiomers.

In summary, we have developed the first enantioselective metal and amine co-catalyzed desymmetrization of 4-propargylamino cyclohexanones for the direct enantioselective synthesis of the morphan core. High enantioselectivity (up to 96% ee) was achieved by exploiting a significant matching effect between the chirality of the 2-bis(aryl)methylpyrrolidine catalyst and a cinchona alkaloid-derived aminophosphine ligand for the silver(I)

co-catalyst. Further work to extend the findings of this study and to apply them in natural product synthesis are underway in our laboratory.

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Keywords: aminocatalysis • asymmetric catalysis • cycloisomerization • morphan core • silver catalysis

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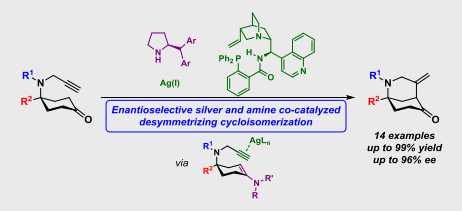
COMMUNICATION



A silver(I) and amine co-catalyzed desymmetrization of 4-propargylamino cyclohexanones for the direct enantioselective synthesis of 2-azabicyclo[3.3.1]nonanes is described. A matching effect between a chiral aminocatalyst and a chiral ligand for silver is exploited. The reaction is efficient, broad in scope and proceeds with high enantioselectivity.

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Enantioselective silver and amine co-catalyzed desymmetrizing cycloisomerization of alkyne-linked cyclohexanones