Asymmetric Catalysis

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Enantioselective Formation of Cyano-Bearing All-Carbon Quaternary Stereocenters: Desymmetrization by Copper-Catalyzed N-Arylation**

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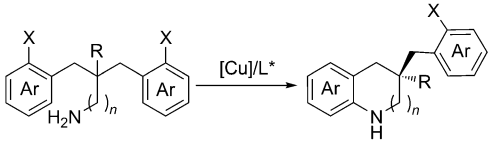
Abstract: *The enantioselective construction of all-carbon quaternary stereocenters is one of the most challenging fields in asymmetric synthesis. An asymmetric desymmetrization strategy offers an indirect and efficient method for the formation of all-carbon stereocenters. An enantioselective formation of cyano-bearing all-carbon quaternary stereocenters in 1,2,3,4,-tetrahydroquinolines and 2,3,4,5-tetrahydro-1H-benzo[b]azepines by copper-catalyzed desymmetric N-arylation is demonstrated. The cyano group at the prochiral center plays a key role for the high enantioselectivity and works as an important functional group for further transformations. DFT studies provide a model which successfully accounts for the origin of enantioselectivity.*

All-carbon quaternary stereocenters are prevalent motifs in a variety of bioactive natural products, pharmaceuticals, and chiral ligands. The enantioselective construction of all-carbon quaternary stereocenters is of great interest to organic chemists because of the features of such structures and the innate synthetic challenge they imply for stereocontrol.[1,2] Despite great efforts devoted to this field, the methods for formation of quaternary stereocenters with excellent enantioselectivity are still quite limited. Only a few direct C–C bond-formation reactions, such as allylic alkylation,[3] conjugation addition,[4] Diels–Alder reactions,[5] [3,3] sigmatropic rearrangement,[6] and so on[7] have been successfully applied to the formation of all-carbon quaternary stereocenters. Novel methods and strategies for the construction of fully substituted carbon centers are badly needed in this field.

Asymmetric desymmetrization,[8] as a means of differentiating two enantiotopic groups in easily accessible starting substances, is an efficient and powerful method for the indirect enantioselective formation of all-carbon quaternary stereocenters. A variety of organocatalytic[9] and transition-metal-catalyzed asymmetric desymmetrization reactions such as palladium-catalyzed coupling,[10] palladium- or rhodium-catalyzed C–H activation,[11] ruthenium- or molybdenum-catalyzed ring-closing metathesis,[12] copper-induced benzoylation,[13] CuAAC,[14] and others,[15] have been successfully implemented in the enantioselective formation of all-carbon quaternary stereocenters.

We recently became interested in the development of transition-metal-catalyzed asymmetric aryl carbon–heteroatom bond-coupling reactions.[16] In 2012, we reported the first copper-catalyzed enantioselective intramolecular N-arylation reaction using a desymmetrization strategy with the assistance of binol-derived ligands.[16a,17,18] This reaction furnished chiral indolines and 1,2,3,4-tetrahydroquinolines bearing N-substituted tertiary or quaternary chiral carbon centers at the 2-position. Encouraged by this success, we explore the potential of our strategy using more intriguing substrates, in which prochiral carbon centers are at either β, λ, or more-remote positions relative to the reactive amine group. These substrates may afford 1,2,3,4-tetrahydroquinoline analogues[19] bearing all-carbon chiral stereocenters at different positions (Scheme 1). The formation of remote all-carbon quaternary stereocenters is much more challenging in comparison to the previous study.[16a] This challenge is due to the inherent steric congestion and diminished chiral bias in a flexible backbone.[1]



Scheme 1. Design of enantioselective formation of all-carbon quaternary stereocenters by desymmetrization through a copper-catalyzed N arylation.

Herein we present enantioselective construction of cyano-bearing all-carbon quaternary stereocenters by desymmetrization using a copper-catalyzed N-arylation with the assistance of a binol-derived ligand.[20]

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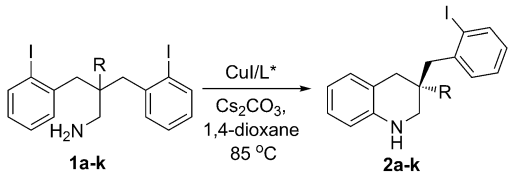
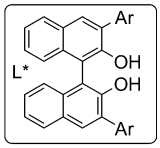
In our previous research,[16a] with the binol-derived ligand **L1**, CuI-catalyzed intramolecular N-arylation gave ester-bearing 2,2-bisubstituted-1,2,3,4-tetrahydroquinolines in excellent yield and enantioselectivity (99% *ee*). Difficulties were encountered however, when we tried to react ethyl 2-(2-iodobenzyl)-2-(aminomethyl)-3-(2-iodophenyl)propanoate (**1a**) to form the ester-containing 3,3-bisubstitstuted-1,2,3,4-tetrahydroquinoline **2a**, which bears an all-carbon stereocenter at the β-position to the reactive amine. Only poor enantioselectivity was obtained at room temperature or at 85 °C (Table 1, entry 1). Moderate enantioselectivity was achieved by switching to another binol-derived ligand, (*R*)-3,3′-di-9-anthracenyl-1,1′-bi-2-naphthol (**L2**; Table 1, entry 2). Such results could be easily understood in terms of the increasing difficulty in the control of enantioselectivity when the chiral carbon center is remote from the reactive site and particularly in the case of an all-carbon quaternary stereocenter. Thus, to improve enantioselectivity, we envisioned that a suitable substituent at the prochiral center would affect the enantioselectivity. A variety of 2-(2-iodobenzyl)-3-(2-iodophenyl)propan-1-amines bearing different functional groups at the prochiral centers were explored (Table 1). The reactions of substrates bearing a hydrogen atom or a methyl group at the prochiral carbon center proceeded smoothly at room temperature with CuI/**L2** to afford the desired coupling products **2b** (56% *ee*) and **2c** (44% *ee*; Table 1, entries 3 and 4). Coupling reactions for other substrates are relatively slow at room temperature, and so the reactions were conducted at elevated reaction temperatures (e.g. 85 °C) for better productivity. Other functional groups, such as amide, dihydrooxazolyl, hydroxy, and carbony units showed inferior results compared to that of an ester group (Table 1, entries 5–9). Finally, we found that a cyano group at the prochiral center enhances both the yield (90%) and enantioselectivity (93% *ee*; Table 1, entry 10). The elevated reaction temperature was highly beneficial to the yield and showed little influence on the enantioselectivity. A similar enantioselectivity (96% *ee*) was obtained in 23% product yield at room temperature (Table 1, entry 11). The absolute configuration of **2i** was determined to be *R* by X-ray crystallography.[21]

Having recognized that the cyano group is critical for high enantioselectivity, we then explored the scope of the substrates. As shown in Table 2, different aryl iodide substrates were examined and all delivered the corresponding products in high yields and good to excellent enantioselectivity. Various functional groups, such as methyl, methoxyl, halide, cyano, and ester groups on the aryl rings were well tolerated

Table 1: Screening of functional groups at the prochiral centers.[a]



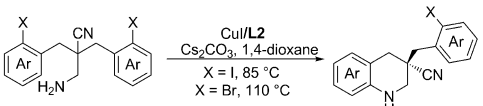


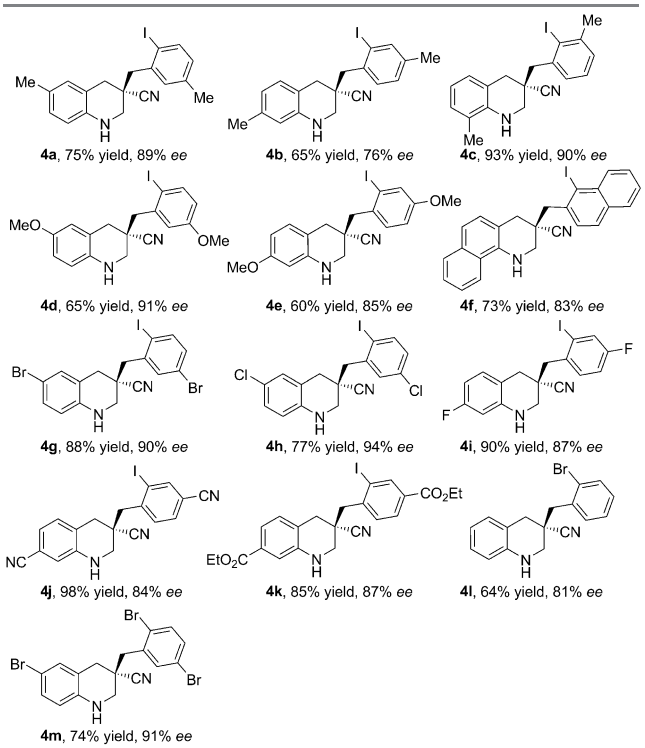
L1: Ar = 3,5-bi(trifluoromethyl)C_6H_3
L2: Ar = 9-anthracenyl

Entry	Substrate	L*	Product	Yield [%][b]	*ee* [%][c]
1	**1a**, R = CO_2Et	**L1**	**2a**	95 (93)	15 (20)[d]
2	**1a,** R = CO_2Et	**L2**	**2a**	89	73
3	**1b**, R = H	**L2**	**2b**	65	56[d]
4	**1c**, R = Me	**L2**	**2c**	60	44[d]
5	**1d**, R = $CONMe_2$	**L2**	**2d**	30	37
6	**1e**, R = dihydrooxazolyl	**L2**	**2e**	63	39
7	**1f**, R = CH_2OH	**L2**	**2f**	70	−37
8	**1g**, R = CH_2OMe	**L2**	**2g**	71	14
9	**1h**, R = COMe	**L2**	**2h**	89	0
10	**1i,** R = CN	**L2**	**2i**	90	93
11	**1i**, R = CN	**L2**	**2i**	23	96[d]

[a] Reagents and reaction conditions: **1a** (0.25 mmol, 1.0 equiv), CuI (0.025 mmol, 10 mol%), **L*** (0.0375 mmol, 15 mol%), Cs_2CO_3, (0.5 mmol, 2.0 equiv), solvent (1 mL), 85 °C, 20 h. [b] Yield of isolated product. [c] Determined by HPLC analysis (Chiralpak AD-H column). [d] Room temperature.

Table 2: Scope of substrates.[a,b,c]

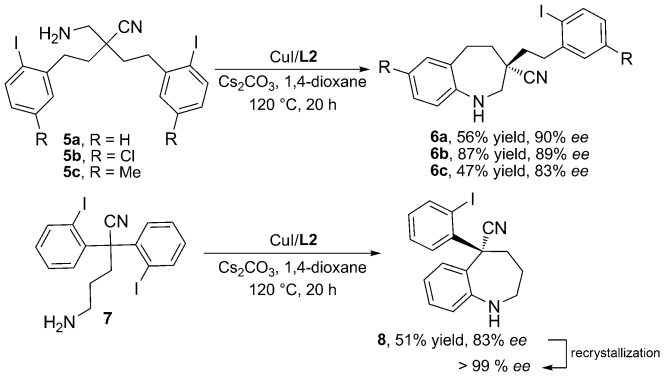




[a] Reagents and reaction conditions: **3** (0.25 mmol, 1.0 equiv), CuI (0.025 mmol, 10 mol%), **L2** (0.0375 mmol, 15 mol%), Cs_2CO_3, (0.5 mmol, 2.0 equiv), 1,4-dioxane (1 mL), 20 h. [b] Yield of isolated product. [c] Enantiomeric excesses were determined by HPLC analysis (Chiralpak AD-H or Chiralcel OD-H column).

(Table 2; **4a–k**). Two aryl bromide substrates were explored and the desired products **4l** and **4m** were also obtained in high yields and high enantioselectivity at a slightly higher reaction temperature of 110 °C.

Encouraged by the above success, we turned our efforts to attain larger ring size and various positions of all-carbon quaternary stereocenters. As shown in Scheme 2, two classes of substrates were explored for the formation of 2,3,4,5-

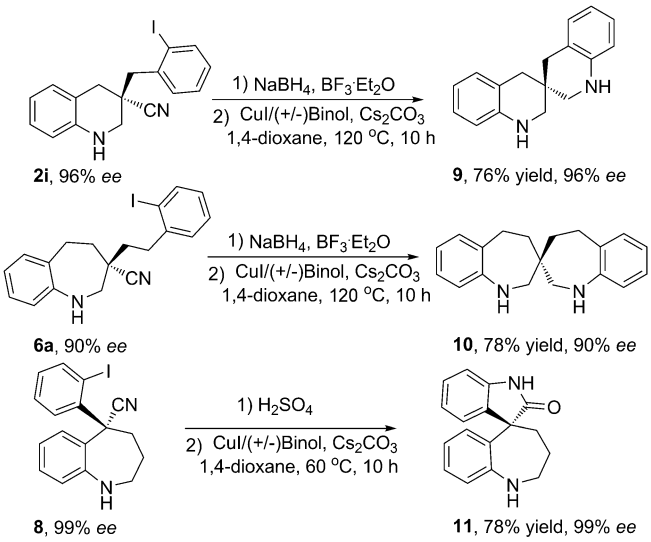


Scheme 2. Enantioselective construction of all-carbon quaternary stereocenters in seven-membered rings.

tetrahydro-1*H*-benzo[*b*]azepines containing a seven-membered ring. First, reactions of the substrates **5a–c**, which retain the prochiral carbon atom at the β-position of reactive amine site, gave **6a–c** in good yields and excellent enantioselectivities at 120 °C. Then, another substrate, **7**, in which the cyano group was installed on the carbon atom bearing two aryl rings, was examined under the same reaction conditions. Despite the steric hindrance at the prochiral center, the desired product **8** was obtained in good yield and with acceptable enantioselectivity (> 99 % *ee* was obtained after one recrystallization).[22]

Following the success in constructing six- and seven-membered rings with all-carbon quaternary stereocenters, we further demonstrated that such products can be easily transformed into interesting [6,6], [7,7] and [5,7] spirocyclic compounds through two steps as shown in Scheme 3.

The mechanism of copper-catalyzed N-arylation of amides has been studied in detail, both experimentally and computationally.[23–25] Here, density functional theory (DFT) calculations were performed to reveal the origin of enantioselectivity.[26,27] Based on a Cu^{I}/Cu^{III} catalytic cycle involving oxidative addition of aryl halide and reductive elimination of the aryl group and nucleophile,[25,28,29] oxidative addition of the C–I bond to the cooper center is expected to determine the enantioselectivity. The transition states leading to *R*- and *S*-configured products are proposed in Figure 1 a. Copper(I) binds to the chiral ligand with an O–Cu dative bond and to the substrate through an amine–copper interaction to form a copper(I) complex.[30] An additional hydrogen bond between the binol and the amine of the substrate positions the substrate in the chiral environment. Before examining the arrangement of the binol and substrate in the transition state (TS), we checked the ground state of substrate first. The most



Scheme 3. Simple transformations towards chiral spriocyclic compounds.

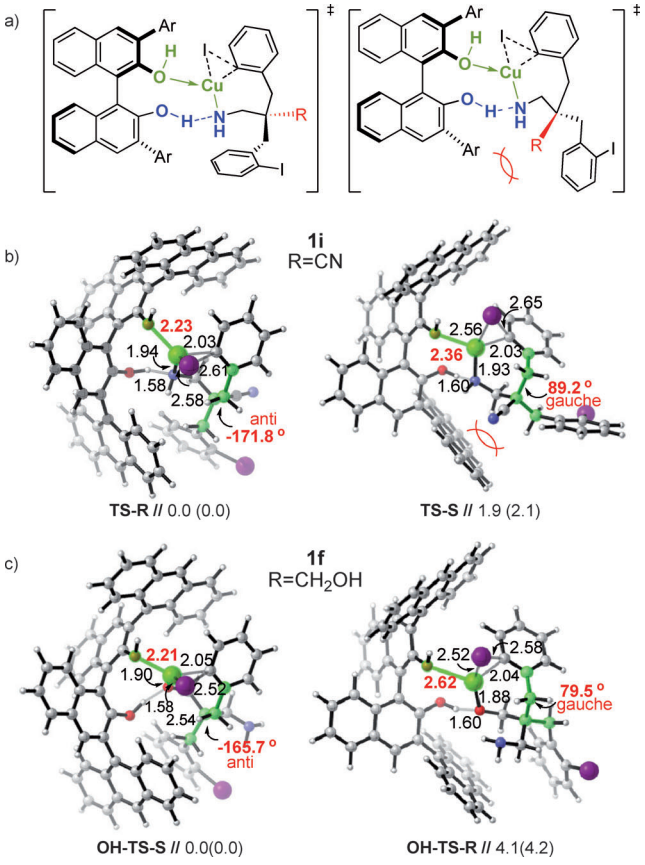


Figure 1. a) Proposed model and optimized transitition states for the enantiodetermining step of the reaction and their relative energies for **1i** (b) and **1f** (c). Relative free energies and energies (within parenthesis) are in kcal mol^{-1}, distances are in Å.

stable conformation of the substrate adopts an extended geometry in which two phenyl groups are on either side of the central line formed by the amine and cyano groups (see Figure S4 in the Supporting Information). In **TS-R**, **1i** can

dock into the chiral pocket without significant conformational change from the ground state (Figure 1b). The cyano group is oriented toward the outer space, while the unactivated phenyl group partially stacks with the anthracenyl group of **L2**. In contrast, for **TS1-S**, the substrate has to employ a less favorable conformation to approach the active center in the chiral environment. As highlighted in Figure 1b, two phenyl groups are oriented in a gauche position. The cyano group in **TS-S** points toward the 9-anthracenyl group. To avoid significant repulsion, the substrate is located farther away from binol. As indicated by the O–Cu distances in **TS-R** (2.23 Å) and **TS-S** (2.36 Å), the binding energy between copper and binol is stronger in the former. As a result, **TS-R** was calculated to be 1.9 kcal mol^{-1} lower in free energy than **TS-S**, and is in good agreement with experimental result of over 90% *ee*. Therefore, this model implicates that the deformation of the substrate and the O–Cu interaction highlighted, can be attributed to the origin of enantioselectivity.

The substrate **1f**, which leads to the opposite enantioselectivity, would be an excellent case to verify the proposed model. The two most stable TSs leading to two enantiomers are shown in Figure 1c. Calculations confirmed that the two stereocontrol factors still operate. However, unlike TSs for the substrate **1i** in Figure 1b, **1f** prefers to coordinate to copper through the hydroxy group rather than the amine. Although the amine is expected to coordinate to copper more strongly, the stronger O–H–O hydrogen bond overrides the coordination preference in the transition state. Because of the change in the coordination group, the *R*/*S* selectivity is switched (see Figure S5 in the Supporting Information). The following selectivity for C–N and C–O coupling has been reported by Fu and co-workers.[25]

So far, our model successfully explains the enantioselectivity qualitatively. The high energy difference between **OH-TS-S** and **OH-TS-R** (Figure 1c) is not quantitatively consistent with the low *ee* value observed experimentally. We postulated that **1f**, containing both OH and NH_2, is a good bidentate ligand which can compete with the chiral **L2** and facilitate the reaction by itself. Therefore, we carried out control experiments to verify this hypothesis. In the absence of **L2**, the racemic N-arylation product from **1f** was indeed obtained with a yield of 35% even at room temperature. However, **1i** does not undergo N-arylation without **L2**. The experimental results support the fact that the background reaction of **1f** can occur and consequently lower the enantioselectivity.

In summary, we have established a desymmetrization reaction through an asymmetric copper-catalyzed N arylation for the enantioselective construction of cyano-bearing all-carbon quaternary stereocenters in 3,3-bisubstituted 1,2,3,4-tetrahydroquinolines and their analogues. In this process, the cyano group plays a key role in generating excellent enantioselectivity. In addition, the cyano group is an important functional group for many subsequent transformations and a variety of interesting spirocycles were synthesized through simple reactions. DFT studies provided a model which successfully accounts for the origin of the enantioselectivity. Further exploration and application of this method in organic synthesis is in progress in our laboratory.

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