Advanced Synthesis & Catalysis

Very Important Publication

Enantioselective Copper-Catalyzed Intramolecular N–H Bond Insertion: Synthesis of Chiral 2-Carboxytetrahydroquinolines

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Abstract: The first highly enantioselective intramolecular N–H bond insertion was realized by using copper catalysts modified with chiral spirobisoxazoline ligands, which provides a novel strategy for the synthesis of chiral 2-carboxytetrahydroquinolines. This reaction features fast reaction rate, high yield, high enantioselectivity, and mild reaction conditions.

Keywords: asymmetric catalysis; carbene insertion; 2-carboxytetrahydroquinolines; chiral spiro ligands; copper

Transition metal-catalyzed carbene insertion into X–H (X = O, N, S, Si, B, etc.) bonds is one of the fundamental reactions for constructing C–X bonds in organic synthesis.[1] In the past decade, catalytic asymmetric X–H insertion reactions have been developed with high enantioselectivities.[2] The highly enantioselective intermolecular N–H bond insertions were accomplished by using chiral copper,[3] rhodium[4] and palladium[5] catalysts or achiral rhodium-chiral phosphoric acid cooperative catalysts.[6] However, the asymmetric intramolecular N–H bond insertion, which provides a potential for the efficient construction of chiral cyclic amines,[7] remains a challenge to date. To the best of our knowledge, only one example for catalytic asymmetric intramolecular N–H insertion reaction was reported by McKervey and coworkers[8] in 1996. By using chiral rhodium(II) carboxylate catalysts, they gained pipecolic acid derivatives in up to 45% *ee*. As a part of our ongoing study on the catalytic asymmetric X–H bond insertion, we here report a highly enantioselective intramolecular N–H bond insertion catalyzed by copper catalysts modified with chiral spirobisoxazoline ligands. The reaction provides a novel strategy for the synthesis of chiral 2-carboxytetrahydroquinolines (Figure 1), which are the ubiquitous building blocks in pharmaceuticals,[9] natural products,[10] and other useful motifs.[11]

Our investigation started from the intramolecular N–H bond insertion of methyl 4-(2-aminophenyl)-2-diazobutanoate (**2a**) using a chiral copper catalyst prepared *in situ* from copper chloride, ligand (S_a,*S*,*S*)-**1a**, and sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($NaBAr_F$) in dichloromethane (DCM) at 25 °C. The reaction was complete in 15 min, affording the product, methyl 1,2,3,4-tetrahydroquinoline-2-carboxylate, in 74% yield with 85% *ee* (Table 1, entry 1). Under otherwise identical reaction conditions, ligand (R_a,*S*,*S*)-**1a** gave only racemic product (entry 2). This result clearly indicated that the ligand (S_a,*S*,*S*)-**1a** had matched chiralities in this reaction.[12] A variety of chiral spirobisoxazoline ligands with different alkyl substituents on the oxazoline ring were compared, and the enantioselectivities gradually decreased with bulkier substituents (entries 3–6). Moreover, the

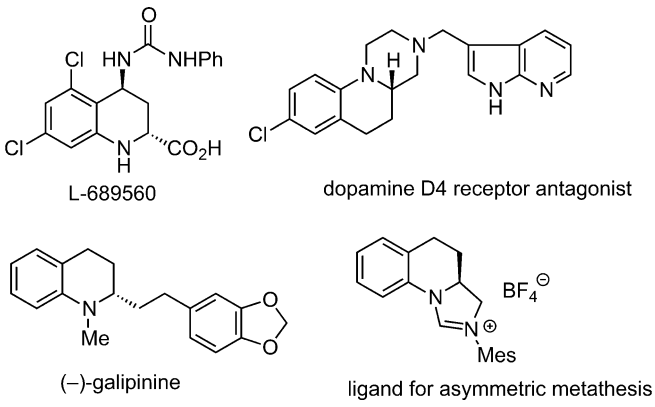
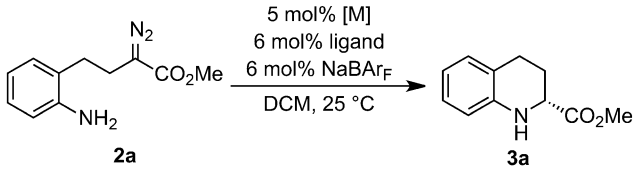
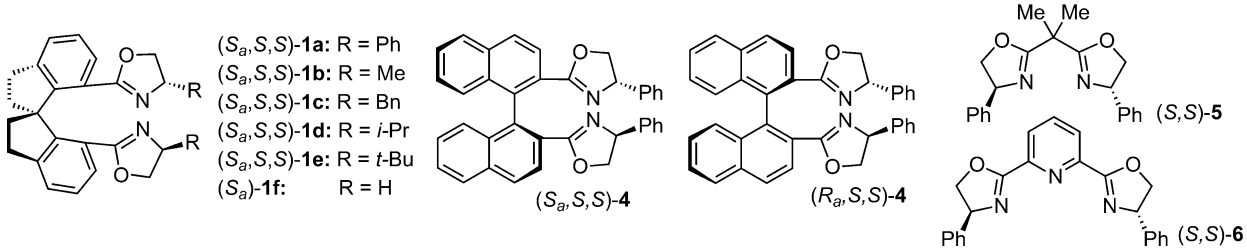


Figure 1. Selected bioactive compounds and ligand with a core structure of chiral tetrahydroquinoline.

Table 1. Copper-catalyzed asymmetric intramolecular N–H bond insertion of **2a**: optimization of the reaction conditions.[a]





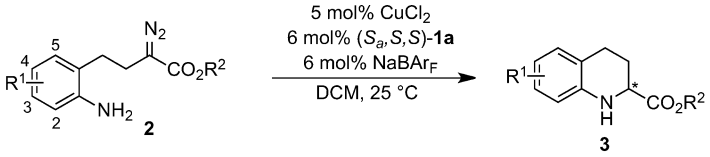
Entry	[M]	Ligand	Solvent	Time [min]	Yield [%][b]	*ee* [%][c]
1	CuCl	(S_a,S,S)-**1a**	DCM	15	74	85
2	CuCl	(R_a,S,S)-**1a**	DCM	10	73	*rac*
3	CuCl	(S_a,S,S)-**1b**	DCM	20	89	77
4	CuCl	(S_a,S,S)-**1c**	DCM	5	84	73
5	CuCl	(S_a,S,S)-**1d**	DCM	5	89	61
6	CuCl	(S_a,S,S)-**1e**	DCM	5	71	28
7	CuCl	(S_a)-**1f**	DCM	120	82	43
8	CuOTf·0.5(toluene)	(S_a,S,S)-**1a**	DCM	5	79	74
9	$Cu(MeCN)_4PF_6$	(S_a,S,S)-**1a**	DCM	5	66	76
10	$CuCl_2$	(S_a,S,S)-**1a**	DCM	5	85	91
11	$CuBr_2$	(S_a,S,S)-**1a**	DCM	5	74	73
12	$CuSO_4$	(S_a,S,S)-**1a**	DCM	over night	71	83
13	$FeCl_2·4H_2O$	(S_a,S,S)-**1a**	DCM	over night	26	*rac*
14	$PdCl_2(PhCN)_2$	(S_a,S,S)-**1a**	DCM	over night	18	*rac*
15	$CuCl_2$	(S_a,S,S)-**1a**	$CHCl_3$	45	89	87
16	$CuCl_2$	(S_a,S,S)-**1a**	DCE	5	78	91
17	$CuCl_2$	(S_a,S,S)-**1a**	toluene	60	71	84
18	$CuCl_2$	(S_a,S,S)-**1a**	THF	5	37	7
19	$CuCl_2$	(S_a,S,S)-**1a**	MeCN	over night	73	*rac*
20	$CuCl_2$	(S_a,S,S)-**4**	DCM	5	75	*rac*
21	$CuCl_2$	(R_a,S,S)-**4**	DCM	5	55	*rac*
22	$CuCl_2$	(S,S)-**5**	DCM	5	98	*rac*
23	$CuCl_2$	(S,S)-**6**	DCM	5	52	8

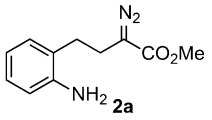
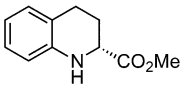
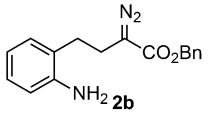
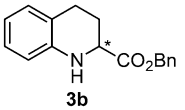
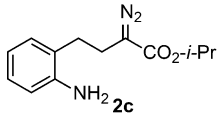
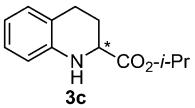
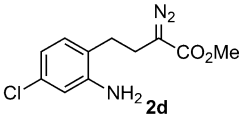
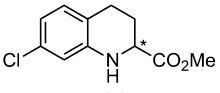
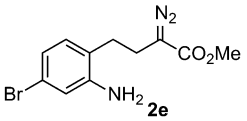
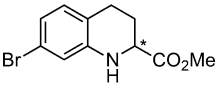
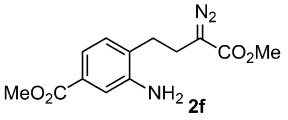
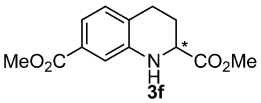
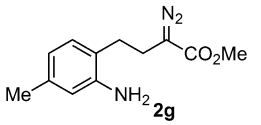
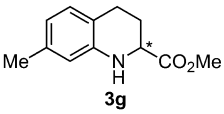
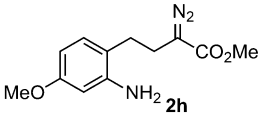
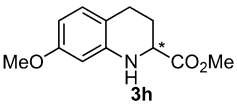
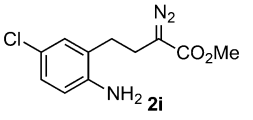
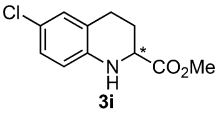
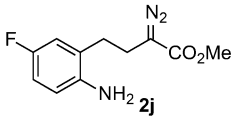
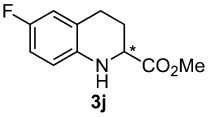
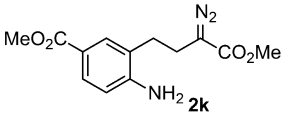
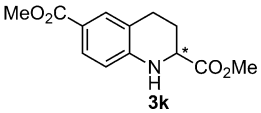
[a] *Reaction conditions:* [Cu]/ligand/$NaBAr_F$/**2a** = 0.02:0.024:0.024:0.4 mmol, in 4 mL solvent at 25 °C.
[b] Isolated yield.
[c] Determined by HPLC using a Chiralcel AD-H column.

ligand (S_a)-**1f** having no substituent at the 4-position of the oxazoline ring, can also give some chiral induction (entry 7). To improve the yield and enantioselectivity of the reaction, we studied various copper catalyst precursors (entries 8–12). All tested copper salts can promote the intramolecular N–H insertion with good to high enantioselectivities, with $CuCl_2$ giving the best result (85% yield, 91% *ee*, entry 10). We also tested iron and palladium salts,[13] but neither exhibited enantioselectivity (entries 13 and 14). In addition to DCM, chloroform and 1,2-dichloroethane (DCE), toluene was also a suitable solvent for the reaction (entries 15–17), while the polar and coordinative solvents tetrahydrofuran and acetonitrile were unsuitable for the reaction (entries 18 and 19). The spirobiindane scaffold of the chiral ligands is crucial for obtaining enantioselectivity.[14] Other chiral bisoxazoline ligands with different backbones gave only racemic product or very low enantioselectivity under otherwise identical reaction conditions (entries 20–23).

The scope of diazo substrates was examined under the optimized reaction conditions (Table 2). The yield and enantioselectivity decreased when a more sterically demanding ester group was employed (entries 1–3). On the other hand, the substituents on the benzene ring of diazoesters **2** also affected the yield and enantioselectivity. The substrates with an electron-withdrawing group (Cl, Br, CO_2Me) at the 3-position

Table 2. Copper-catalyzed asymmetric intramolecular N–H bond insertion: substrate scope.[a]



Entry	Diazo compound	Product	Time [min]	Yield [%]	*ee* [%]
1	 **2a**	 **3a**	5	85	91 (*R*) [b]
2	 **2b**	 **3b**	30	81	88
3	 **2c**	 **3c**	30	71	84
4	 **2d**	 **3d**	5	90	96
5	 **2e**	 **3e**	5	87	93
6	 **2f**	 **3f**	360	57	90
7	 **2g**	 **3g**	5	80	86
8	 **2h**	 **3h**	5	79	83
9	 **2i**	 **3i**	5	87	96
10	 **2j**	 **3j**	15	65	76
11	 **2k**	 **3k**	15	92	86

[a] The reaction conditions and analyses were the same as those in Table 1, entry 10.
[b] The absolute configuration was determined by comparing the specific optical rotation with the reported data.[15]

of the benzene ring generally afforded high enantioselectivity (90–96% *ee*, entries 4–6), albeit the one with 3-CO_2Me required a longer reaction time (6 h) for full conversion and gave lower yield. On the contrary, when an electron-donating group was introduced at the 3-position of the benzene ring, the enantioselectivity decreased (entries 7 and 8). The substituents at the 4-position of the benzene ring also significantly affected the outcomes of the reaction: the chloro substituent gave excellent enantioselectivity (96% *ee*, entry 9), while the fluoro and ester substituents afforded lower enantioselectivity (76% *ee* and 86% *ee*, respectively, entries 10 and 11). The absolute configuration of **3a** was determined to be *R* by comparing the specific optical rotation with the reported data (entry 1).[15]

In summary, we have developed a highly enantioselective copper-catalyzed intramolecular N–H bonds insertion reaction, which provided a new method for the synthesis of chiral 2-carboxytetrahydroquinolines. The fast reaction rate, high yield, high enantioselectivity of the reaction further demonstrate the power of these catalytic asymmetric X–H bond insertion reactions in organic synthesis.

Experimental Section

Typical Procedure for Copper-Catalyzed Asymmetric Intramolecular N–H Bond Insertion

$CuCl_2$ (2.7 mg, 0.02 mmol, 5 mol%), (S_a,*S*,*S*)-**1a** (8.6 mg, 0.024 mmol, 6 mol%) and $NaBAr_F$ (22.6 mg, 0.024 mmol, 6 mol%) were added into an oven-dried Schlenk tube. CH_2Cl_2 (3 mL) was injected *via* syringe and the mixture was stirred at 25 °C for 2 h, followed by addition of the diazo compound **2a** (0.4 mmol, dissolved in 1 mL of CH_2Cl_2). The resulting mixture was stirred for 5 min. After removing the solvent under vacuum, the residue was chromatographed on silica gel (petroleum ether/ethyl acetate = 8:1) to give product **3a** as a colorless oil; yield: 85%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01 (t, *J* = 7.7 Hz, 1H), 6.97 (d, *J* = 7.4 Hz, 1H), 6.66 (t, *J* = 7.1 Hz, 1H), 6.60 (d, *J* = 8.0 Hz, 1H), 4.37 (s, 1H), 4.05 (dd, *J* = 8.8 and 3.7 Hz, 1H), 3.78 (s, 3H), 2.90–2.70 (m, 2H), 2.35–2.24 (m, 1H), 2.08–1.95 (m, 1H); 91% *ee* by HPLC (conditions: Daicel AD-H column, *n*-hexane/2-propanol = 90:10, flow rate = 1.0 mL min^{-1}, wavelength = 254 nm): t_R = 8.65 min for major isomer, t_R = 10.30 min for minor isomer; $[\alpha]_D^{22}$: −37.9 (*c* 1.05, $CHCl_3$); Lit.[15] $[\alpha]_D$: −33.9 (*c* 0.36, $CHCl_3$) for (*R*)-**3a**.

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