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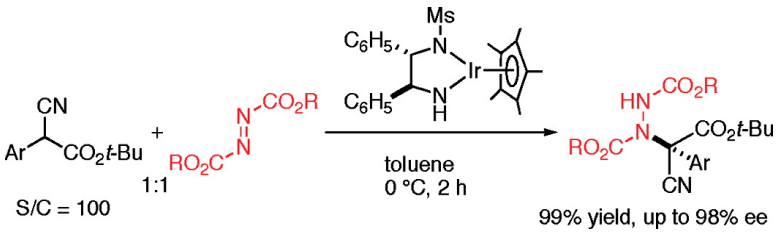

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Enantioselective Direct Amination of α-Cyanoacetates Catalyzed by Bifunctional Chiral Ru and Ir Amido Complexes

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The catalytic, enantioselective, and direct C−N bond formation using unmodified nucleophiles and a nitrogen source such as azodicarboxylates would offer a simple and straightforward procedure for construction of a stereogenic carbon center attached to a nitrogen atom.[1] There are many reports on enantioselective direct amination via C−N bond forming reaction catalyzed by chiral catalyst systems. They include chiral Lewis acid catalysts for direct α-amination of β-keto esters,[2a−c] and pyruvic acid derivatives,[2d] and chiral organocatalysts for α-amination of aldehydes,[3a−d,m] ketones,[3e−g] and β-keto esters,[3h−j] or α-substituted α-cyanoacetates.[3k,l] In particular, the electrophilic amination of α-substituted β-keto esters or α-substituted α-cyanoacetates provides an attractive procedure to access chiral nitrogen-containing compounds bearing a quaternary carbon center. Among these enantioselective methods, only a very limited number of chiral metal-based catalytic asymmetric direct aminations have been reported.[2,4] We have recently developed a conceptually new bifunctional chiral amido transition-metal catalyst, Ru(Tsdpen)(η^6-arene)[5] (TsDPEN: *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) (**1**), for a catalytic asymmetric Michael reaction of 1,3-dicarbonyl compounds to cyclic enones and nitro alkenes.[6] The Brønsted basic amide catalyst is responsible for high reactivity and selectivity in the enantioselective C−C bond formation. We have extended the concept of the bifunctional molecular catalysis to the C−N bond-forming reaction and found that the electrophilic direct amination of α-substituted α-cyanoacetates using dialkyl azodicarboxylates with a chiral amido Ir complex, Cp*Ir(Tsdpen)[7] (**2b**), which has a structure isoelectronic with **1**, proceeded smoothly to provide the corresponding hydrazine adducts in high yields and with excellent ee values.

A chiral amido Ir complex (*S,S*)-**2a**[7] has proven to effect efficient asymmetric amination of *tert*-butyl α-phenyl-α-cyanoacetate (**3a**) using dimethyl azodicarboxylate (**4a**) (a substrate/catalyst ratio, S/C = 100, **3a**/**4a** = 1:1) in a 0.1 M toluene solution at 0 °C for 2 h to furnish the corresponding adduct in an excellent yield, 99% and with 85% ee (Scheme 1). Since the uncatalyzed reaction of **3a** and **4a** under otherwise identical condition gave the racemic product, **5a**, quantitatively, it can compete with the catalytic enantioselective reaction, leading to low enantioselctivity. Noticeably, a slow addition of azodicarboxylate, **4**, to a toluene solution of **3** containing the Ir catalyst with a syringe pump for 20 min at 0 °C followed by stirring of the reaction mixture for 2 h improved significantly the ee value of the product, reaching 95% ee as listed in Table 1. Decreasing the reaction temperature to −40 °C resulted in an additional increase in the ee value of **5**, to 97%. In contrast to the Ir system, the chiral Ru complex, Ru[(*S,S*)-PMsdpen](η^6-hmb) (PMs = $C_6(CH_3)_5SO_2$, HMB = hexamethylbenzene) (**1a**),[6b] exhibited unsatisfactory enantioselectivity even after structural optimization of the Ru catalyst (see Supporting Information).

Scheme 1

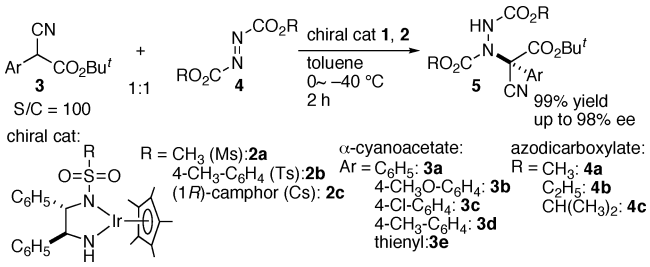

Table 1. Asymmetric Amination of α-Substituted α-Cyanoacetates Using Azodicarboxylates Catalyzed by Chiral Amide Complexes[a]

chiral catalyst	cyano-acetate	azo-dicarboxylate	solvent	temp °C	yield %[b]	ee %[c]
	3a	**4a**	toluene	0	99	
1a	**3a**	**4a**	toluene	0	99	66
2a	**3a**	**4a**	toluene	30	99	90
2a	**3a**	**4a**	toluene	0	99	95
2a	**3a**	**4a**	toluene	−40	99	97
2b	**3a**	**4a**	toluene	0	99	89
2c	**3a**	**4a**	toluene	0	99	98
2a	**3a**	**4a**	THF	0	99	83
2a	**3a**	**4a**	$C_2H_5(CH_3)_2COH$	0	99	83
2a	**3a**	**4a**	acetone	0	99	73
2a	**3a**	**4a**	CH_2Cl_2	0	99	67
2a	**3a**	**4a**	CH_3CN	0	99	10
2a	**3a**	**4b**	toluene	0	99	91
2a	**3a**	**4c**	toluene	0	99	66
2a	**3b**	**4a**	toluene	0	99	91
2a	**3c**	**4a**	toluene	0	99	95
2a	**3d**	**4a**	toluene	0	99	96
2a	**3e**	**4a**	toluene	0	99	95

[a] Unless otherwise noted, the reaction was carried out by a slow addition of **4** to a toluene solution of **3** containing the chiral amide catalyst with a syringe pump for 20 min followed by stirring for 2 h in 5 mL solvent. The molar ratio of metal/azodicarboxylate/cyanoacetate is 1:100:100 (see Supporting Information). [b] Isolated yield after flash chromatograpgy on silica gel. [c] Determined by HPLC analysis using CHIRALPAK AD (4.6 mm × 250 mm).

The stereochemical outcome of the reaction with the chiral Ir catalyst was delicately influenced by the structures of the Ir complexes as well as reaction conditions (Table 1). The TsDPEN complex **2b** provided lower enantioselectivity, while the CsDPEN complex **2c**[7b] gave the best catalyst performance in terms of the selectivity, the ee value of the product reaching up to 98% ee. Toluene, $C_2H_5(CH_3)_2COH$, and THF worked well, while CH_2Cl_2 and acetone gave a slightly lower ee values. The enantioselectivity of the reaction in CH_2Cl_2 improved significantly when the reaction mixture was cooled down to −40 °C, the ee value reaching up to 92%. Notably, acetonitrile gave unsatisfactory results possibly due

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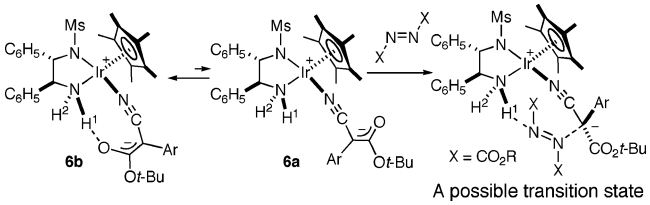
Scheme 2



to its strong bonding ability toward the metal center.[8] An increase in the steric bulkiness in the ester group of **4** caused a decrease in the ee value of the products. The aromatic ring-substituted α-phenyl-α-cyanoacetates (**3b**−**d**) reacted with **4a** in toluene containing chiral Ir catalyst at 0 °C for 2 h to give the chiral adduct with 91−96% ee in excellent yields regardless of the electronic effect of the substituent. Similarly, α-cyanoacetate with thienyl group (**3e**) provided the adduct with 95% ee.[3k]

A stoichiometric reaction of the amido Ir complex with *tert*-butyl α-cyanoacetate **3a** provided further insight into the reaction mechanism. The reaction of **3a** with the amido Ir complex, **2a** (**2a**/**3a** = 1:1−1.5) in CH_2Cl_2 proceeded rapidly to give a mixture of two N-bound nitrile complexes, Cp*Ir[NCC(C_6H_5)(COOC(CH_3)$_3$)]-[(*S*,*S*)-Msdpen] (**6a**,**b**) (Scheme 2). ^{1}H and ^{13}C NMR spectra of the reaction mixture at −50 °C showed two sets of sharp signals due to **6a** and **6b**.[9] The assignment of signals in the ^{1}H NMR spectrum was accomplished by the COSY experiment. Two NH_2 protons in the ^{1}H spectrum of the minor isomer **6a** resonate at δ 4.02 (triplet, *trans* to the CHC$_6$H$_5$) and 4.48 (doublet, *cis* to the CHC$_6$H$_5$). In the ^{1}H NMR spectrum of the major isomer **6b**, the corresponding doublet resonates very close to that of **6a** (δ 4.22), whereas the triplet is strongly downfield shifted (δ 6.21), indicating the presence of the intramolecular hydrogen bond in **6b** that is absent in **6a**.[9] On raising the temperature, the signals in the ^{1}H and ^{13}C NMR spectra of **6a** and **6b** broadened reversibly, indicating that **6a** and **6b** are equilibrating in solution. The IR spectrum of **6** in KBr showed that a CN stretching band appears at 2174 cm^{-1}, which is lower than that in free cyanoacetate (2263 cm^{-1}), indicating that **6** has a structure bearing the N-bonded nitrile group, as observed in the reported cyanoester complexes.[10]

On the basis of the absolute configuration, *R*, of the α-aminated product[3l] and the results of a combined NMR[9] and computational (B3LYP/SDD) analysis (Supporting Information), we concluded that the enantioselection in the reaction may occur through a concerted formation of C−N and H−N bonds taking place in the N-bound cyanoester complex **6a** as shown in Scheme 2. The azodicarboxylate might approach the N-bound cyanoester anion by interaction of incoming nitrogen atom with the NH proton of the amino group in the Ir complex **6a**. On the other hand, the intramolecular hydrogen bonding to the equatorial NH proton in the conformer **6b** cannot participate in the formation of a similar transition state. Thus, the reactants **3** and **4** are activated sequentially by the bifunctional catalyst to facilitate the enantioselective C−N bond forming reaction.

In summary, the bifunctional chiral amido Ir complex **2** catalyzed asymmetric electrophilic direct amination of α-substituted α-cyanoacetates using azodicarboxylates proceeds rapidly to provide the corresponding hydrazine adducts in high yields and with excellent ee values. The deprotonation of cyanoacetates with the chiral amide complex would lead to the formation of the N-bound nitrile complexes. We are now working on further expansion of the substrate scope and further studies aimed at clarifying the mechanism.

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Supporting Information Available: Experimental procedures of the catalytic direct amination reaction, spectroscopic data for compounds, and NMR and computational (B3LYP/SDD) analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) ^{13}C NMR and DEPT spectra at −50 °C showed that the deprotonated anionic carbon resonates at δ 58.6 in **6b** (anionic carbon for minor product **6a** had not been observed), whereas the metal-bonded nitrile carbon atom appears between δ 135.2 and 140.2 in **6b** and δ 137.1 and 139.2 in **6a**, which is notably down-field shifted compared to free **4** (δ 116.0).

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