Synthetic Methods

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Enantioselective and *Z*/*E*-Selective Conjugate Addition of α-Substituted Cyanoacetates to Acetylenic Esters Catalyzed by Bifunctional Ruthenium and Iridium Complexes**

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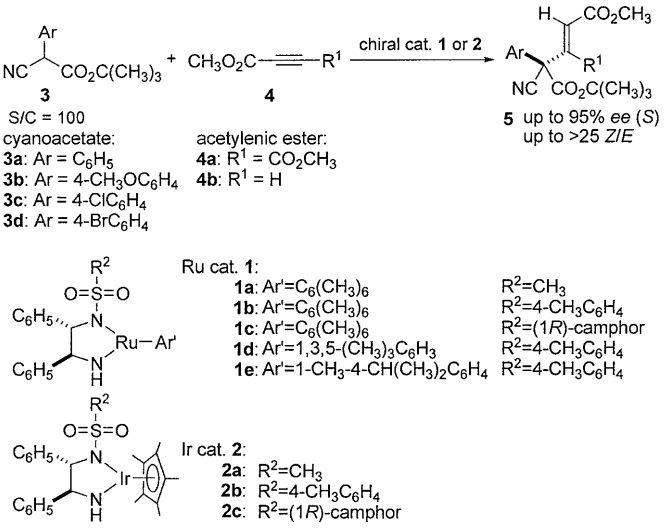
Catalytic and stereoselective formation of quaternary carbon centers remains a significant challenge in organic synthetic chemistry.[1] Metal-based catalytic methods including asymmetric alkylation and arylation of carbonyl compounds as well as enantioselective Diels–Alder reactions have been successfully applied for the creation of compounds with chiral quaternary carbon centers.[2] Asymmetric conjugate addition of pronucleophiles to α,β-unsaturated carbonyl groups presents one of the most powerful and atom-economic synthetic approaches to access enantiomerically enriched quaternary carbon skeletons for the synthesis of biologically active compounds. However, the chiral metal-based catalyst systems for enantioselective conjugate addition remain relatively rare, being limited to multimetal chiral catalysts[1f,g,3] and chiral metal–enolates.[4] Our research group has developed a highly efficient asymmetric conjugate addition of 1,3-dicarbonyl groups to cyclic enones and nitroalkenes with our bifunctional chiral amido Ru catalysts **1**[5] [Ru(Tsdpen)(η^6-arene)] (Tsdpen: *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine).[6] The use of α-cyanoacetate as a pronucleophile combined with diazoesters in the presence of bifunctional chiral Ir amido catalysts **2**[7] [Cp*Ir(Tsdpen)] (Cp* = η^5-$C_5(CH_3)_5$) also resulted in the direct amination of activated cyanoacetate to provide products with enantiomerically enriched tertiary carbon centers.[8] Preliminary mechanistic studies showed that the key stage of the catalytic cycle is the deprotonation of the acidic pronucleophile with the chiral amido catalyst which leads to the stereoselective formation of an N-bound amine complex.[6c] The resulting amine complex bearing a metal-bound nucleophile readily reacts with suitable electrophiles to give C–N bond-formation products in a highly stereoselective manner.[8] We reasoned that other electrophiles may also react with this catalyst–substrate complex in a similar way to afford new enantioselective catalytic transformations. Herein, we report an enantioselective and *Z*/*E*-selective catalytic C–C bond-forming reaction between α-substituted cyanoacetates and acetylenic esters using bifunctional Ru (**1**) and Ir (**2**) catalysts to yield chiral adducts having a quaternary carbon center. Moreover, NMR and computational studies revealing the origin of enantioselectivity in this reaction are also reported.

We have found that the conjugate addition of cyanoacetate **3** to acetylenic diester **4a** in the presence of bifunctional Ru (**1**) or Ir (**2**) catalysts (cyanoacetate/acetylenic ester/cat. = 100:100:1) at 0 °C gave the corresponding chiral adducts **5** with good to excellent enantiomeric excess and *Z*/*E* selectivity in almost quantitative yields (Scheme 1). Table 1 lists representative results for the reaction (see the Supporting Information for more details). Chiral Ru and Ir complexes work equally well for this reaction, in contrast to the reaction of cyanoacetate **3a** and diazoesters,[8] in which the chiral Ir catalyst was far superior to the Ru catalyst.



Scheme 1. Enantioselective reaction of α-cyanoesters and acetylenic esters. Reaction carried out with a 1:1 ratio of substrates. S/C: substrate to catalyst ratio.

As seen in Table 1, the stereochemical outcome of the reaction is significantly influenced by the structures of the catalysts as well as the reaction conditions. The optimal catalysts are **1b** and **2b** with the Tsdpen ligand (entries 1 and 2; aryl = hexamethylbenzene for the Ru catalyst and aryl = Cp* for the Ir catalyst). Other Ru complexes with mesitylene (**1d**) and *p*-cymene (**1e**) aryl groups gave unsatisfactory

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Table 1: Results of the enantioselective addition of cyanoacetates **3** to acetylenic esters **4** promoted by chiral catalysts **1** or **2**.[a]

Entry	Cyanoacetate	Acetylenic ester	Cat.	Solvent	Yield [%][b]	*Z*/*E*	*ee* [%] (*Z*/*E*)[c]
1	**3a**	**4a**	**1a**	toluene	97	20/1	86/22
2	**3a**	**4a**	**1b**	toluene	97	20/1	91/52
3	**3a**	**4a**	**1c**	toluene	98	23/1	83/25
4	**3a**	**4a**	**1d**	toluene	97	14/1	79/13
5	**3a**	**4a**	**1e**	toluene	97	6/1	43/04
6	**3a**	**4a**	**1b**	CH_2Cl_2	98	2/1	82/81
7	**3a**	**4a**	**1b**	$Et(Me)_2COH$	99	2/1	72/72
8	**3a**	**4a**	**2a**	toluene	96	20/1	84/10
9	**3a**	**4a**	**2b**	toluene	96	20/1	90/23
10	**3a**	**4a**	**2c**	toluene	95	23/1	81/10
11	**3b**	**4a**	**1b**	toluene	98	20/1	89/n.d.
12	**3c**	**4a**	**1b**	toluene	99	17/1	92/27
13	**3d**	**4a**	**1b**	toluene	99	20/1	95/05
14	**3a**	**4b**	**1b**	toluene	99	1/22	n.d./79
15	**3a**	**4b**	**1b**	CH_2Cl_2	99	1/2	65/79
16	**3a**	**4b**	**1b**	CH_3CN	99	1/2	0/0

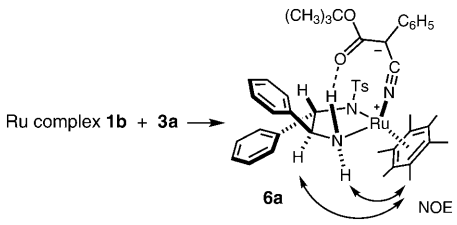
[a] Unless otherwise noted, the reactions were carried out by the slow addition of **4** with a syringe pump to a solution of **3** and the chiral amido catalyst in 5 mL of solvent for 20 minutes and subsequent stirring for 24 hours. The molar ratio of cyanoacetate/acetylenic ester/catalyst = 100:100:1. [b] Yield of isolated product after column chromatography on silica gel. [c] Determined by HPLC on a chiral stationary phase using a Chiralpak AD-H column (4.6 mm × 250 mm). n.d. = not determined.

results in terms of enantioselectivity and the *Z*/*E* selectivity (entries 3–5). Choice of the solvent has a significant influence on the configuration of the products. Nonpolar solvents like toluene or dichloromethane gave high enantioselectivity, while polar solvents lead to a dramatic decrease of the *ee* values and the *Z*/*E* selectivities (entries 2, 6, and 7). The α-phenyl-α-cyanoacetates (**3b–d**), which have substituted aromatic rings, reacted with **4a** in toluene catalyzed by the chiral Ru catalyst (**1b**) at 0 °C for 24 hours and gave the chiral adduct with 89–95 % *ee* in excellent yields regardless of the electronic effect of the substituents (entries 11–13). The reaction of cyanoacetate **3a** and the acetylenic monoester **4b** with the chiral Ru catalyst **1b** gave the corresponding adduct with excellent *E* selectivity albeit with modest *ee* values (entries 14–16). Thus, our approach provides sufficiently high *ee* values with much higher *Z*/*E* ratios than those of the reported reaction promoted by organocatalysts.[9]

To gain further insight into the reaction mechanisms, we elucidated the structure of the intermediate, N-bound Ru catalyst–substrate complexes **6a** and **6b** in solution (Scheme 2). The reaction of complex **1b**[10] with α-cyanoacetate **3a** yielded the equilibrium mixture of **6a** and **6b** in a reversible and stereoselective manner—as was observed previously with chiral Ir complexes.[8] From the ^{13}C DEPT and HMBC spectra measured at −55 °C, we have located the positions of nonprotonated carbon atoms of **6a**,**b** in the ^{13}C NMR spectrum. The deprotonated anionic carbon atoms resonate at $\delta = 58.7$ ppm and $\delta = 56.5$ ppm in **6a** and **6b**, respectively. Whereas the nitrile carbon atom is notably shifted downfield compared to free substrate **3a** ($\delta =$ 136.7 ppm in **6a** versus $\delta = 117.3$ ppm in **3a**). These data confirm N-binding of the substrate in **6a**,**b**.[8]

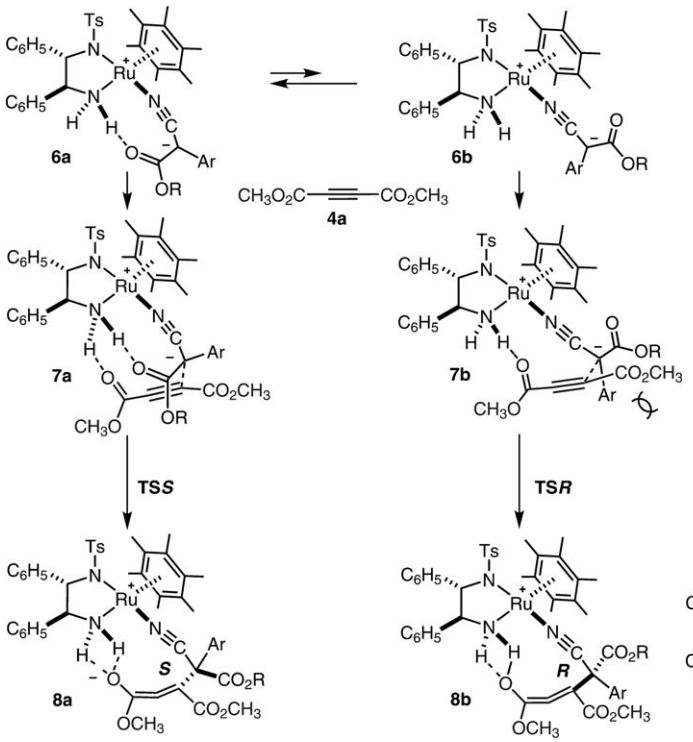
In computational work we have located adducts **7a** and **7b** in which the substrate **4a** is activated in a concerted manner by **6a** or **6b**, respectively (Scheme 3). In these adducts, the orientation of the acceptor toward the amine complex bearing cyanoacetate anion, **6a** or **6b**, has a critical importance for determining the enantioselectivity. Noticeably, the enantioface of the N-bound cyanoacetate anion used for the coordination of substrate is opposite for both adducts: *Si* face for **7a** and *Re* face for **7b**. Hence, the C–C bond formation would yield intermediates **8a** and **8b**—with opposite configuration at the benzylic carbon atoms—which are precursors of the products (*S*)-**5a** and (*R*)-**5a**, respectively.

For the computational study, we have used the Ru–Tsdpen complex **1b** because it provides slightly better enantioselectivities than **2a**. We have optimized the structures of



Scheme 2. NOE interactions observed in the phase-sensitive 2D ^1H–^1H NOESY spectrum (400 MHz, CD_2Cl_2, 223 K) of the sample prepared by the addition of 1.5 equivalents of cyanoacetate **3a** to the amido Ru complex **1b**. See the Supporting Information for more details. Ts = 4-toluenesulfonyl.

the adducts **7a** and **7b** and found two viable transition states (**TS*S*** and **TS*R***, respectively) for the C–C bond-formation step that would each proceed to the intermediates **8a**,**b** (Scheme 3, Figure 1). Formation of either **7a** or **7b** is exothermic; they have similar structures appropriate for the concerted activation. However, **7b** is 9.4 kcal mol^{-1} less stable than **7a**. This difference in the stability originates from the steric interactions of the loose carbomethoxy group with the substituents on the anionic carbon atom. Similarly, owing to the smaller steric interactions of the *tert*-butoxycarbonyl substituent, the transition state of the C–C bond-formation step resulting in the *S* product is 9.7 kcal mol^{-1} lower in energy compared to the unfavorable transition state that leads to the *R* product. Thus, we have found a structural reason for the strong bias towards the enantioselective formation of the *S* product that is in accord with the experimentally determined sense of enantioselection. The experimental *ee* values are, however, lower than might be expected in view of such a substantial energy difference. This outcome might be



Scheme 3. Alternative pathways for C–C bond formation leading to different enantiomers of the reaction product. R = $C(CH_3)_3$.

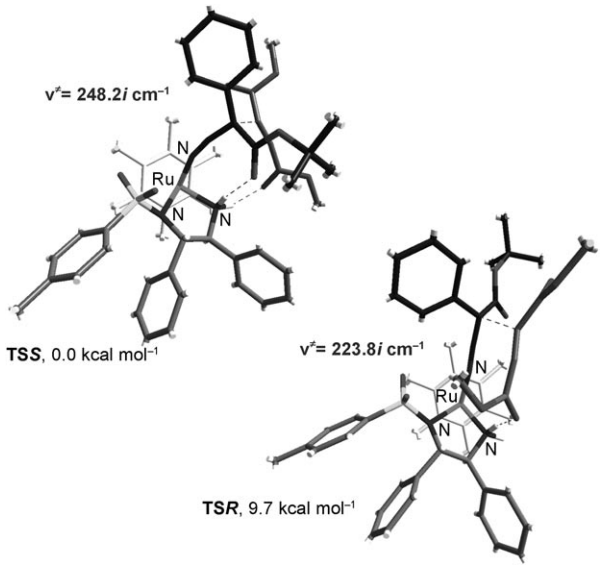
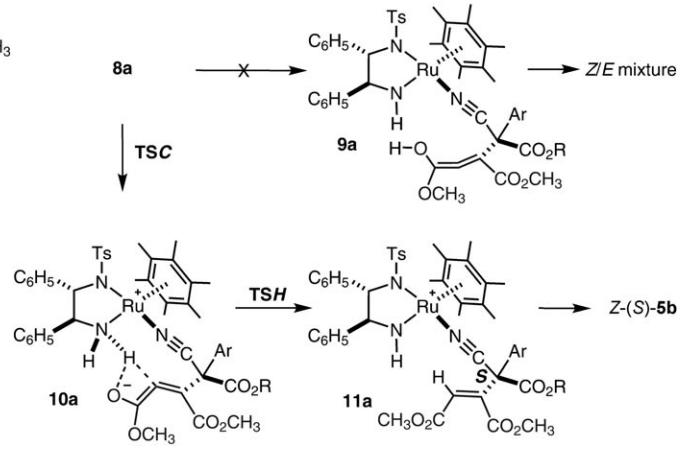


Figure 1. Optimized structures of the transition states **TS*R*** and **TS*R***. Computational studies were performed at the B3LYP/SDD level of theory with an additional diffuse function for sulfur. The $v^{\neq}$ values are imaginary frequencies for the transition states. The activation energies for the C–C bond-formation steps were computed to be 11.6 and 11.9 kcal mol^{-1} for the *S* and *R* configurations, respectively.

explained by the interference from the noncatalyzed reaction and nonstereoselective activation pathways.

The high *Z*/*E* ratios of the reaction product suggest that the proton transfer occurs directly from the nitrogen atom to the carbon atom, because protonation of the oxygen atom would yield a hydroxyallene intermediate **9a** with equal potential for transferring the proton to two alternative positions (Scheme 4). We have located a transition state for the direct proton transfer from the bent allenic intermediate **10a** to the catalyst product, namely complex **11a** (Scheme 4). The detailed computational study of the internal rotation in the allenic fragment transforming **8a** to **10a**, which have bent structures owing to 1,1-oxo substitution,[11,12] will be reported in a full paper.



Scheme 4. *Z*-selective proton transfer from the amine nitrogen atom to the allenic carbon atom. R = $C(CH_3)_3$.

In summary, the bifunctional chiral amido Ru and Ir complexes have efficiently promoted the catalytic asymmetric conjugate addition of α-substituted cyanoacetates to acetylenic esters to provide the corresponding chiral adducts in high yields and with excellent *ee* values and *Z*/*E* selectivity. The deprotonation of cyanoacetates using the chiral amido complex would lead to the formation of the N-bound nitrile complexes bearing a cyanoacetate anion. The enantioselective C–C bond formation occurs through the sterically favorable coordination of the acetylenic ester to the N-bound complex **6a**. The subsequent proton transfer occurs intramolecularly, resulting in the high *Z*/*E* selectivity of the reaction.

Experimental Section

General experimental procedure for the conjugate addition: Under an argon atmosphere at 0 °C, **4a** (62 μL, 0.50 mmol) was added slowly (over 20 min using a syringe pump) to a solution of **3a** (108 mg, 0.50 mmol) in toluene (5 mL) containing the amido catalyst **1a** (3.1 mg, 5 mmol). The reaction mixture was then stirred for 24 h at 0 °C. The molar ratio of cyanoacetate/acetylenic ester/catalyst = 100:100:1. After evaporation of the solvent with a vacuum pump, the crude product was purified with by column chromatography on silica gel (eluent: *n*-hexane/ethyl acetate 99:1) to give the desired adduct **5a** with a *Z*/*E* ratio of 20:1 in 97% yield (348 mg). The *ee* value of the major isomer was 91% *ee*. All products were analyzed and the *Z*/*E* ratios were determined by ^{1}H NMR spectroscopy. The *ee* values were determined by HPLC on a chiral stationary phase using a Chiralpak AD-H column. Spectroscopic data for the hydrogenated products are provided in the Supporting Information. The absolute configuration and the structure of the *Z* isomer were

determined by single-crystal X-ray crystallographic analysis. CCDC 780649 (**5a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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