Asymmetric Catalysis

DOI: 10.1002/anie.201100252

C_1-Symmetric Rh/Phebox-Catalyzed Asymmetric Alkynylation of α-Ketoesters**

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Catalytic asymmetric alkynylation of carbonyl compounds is one of the most efficient routes for the synthesis of optically active propargylic alcohols, which are useful and versatile building blocks for a variety of functionalized molecules, such as biologically active natural products.[1] In the initial stages of development of this transformation, stoichiometric amounts of metal reagents such as organolithium, organomagnesium, and diorganozinc compounds were used to increase the nucleophilicity of the alkyne and to prevent an undesired retro reaction.[1,2] In terms of atom economy,[3] however, the direct in situ generation of a metal alkynylide species from terminal alkynes using a catalytic amount of the metal reagent is highly desirable. Since the pioneering work by Carreira and co-workers, who utilized catalytic amounts of $Zn(OTf)_2$, *N*-methylephedrine, and Et_3N,[4] several efficient methods for the catalytic asymmetric alkynylation of aldehydes have been developed using chiral Zn,[5] In,[6] Cu,[7] and Ru[8] catalysts.[9]

In contrast to the substantial progress made with aldehydes, the development of a catalytic asymmetric alkynylation of ketones for the construction of a tetrasubstituted carbon center in an enantioselective manner has had limited success due to low reactivity, difficulty in obtaining enantiofacial differentiation, and the ease of the retro reaction as compared with aldehydes.[10] Jiang et al. succeeded in promoting the asymmetric alkynylation of α-ketoesters with broad substrate scope and high enantioselectivity (up to 94% *ee*)[11a] by modifying Carreira's Zn system.[4] Later, Shibasaki and co-workers reported Cu catalysis of trifluoromethyl ketone with up to 52% *ee*,[11b] and the Rh catalysis of an α-diketone reported by Chisholm and co-workers gave the product in 5% yield with 20% *ee*.[11c] Although the method of Jiang et al. is useful for accessing chiral propargylic alcohols, there remains much room for improvement because this system requires 20 mol% catalyst loading, 30 mol% of external amine base, and a rather high reaction temperature (70 °C).[11a] Herein, we report the catalytic asymmetric alkynylation of α-ketoester **1** using various aryl- and alkyl-substituted terminal alkynes **2** catalyzed by as little as 3 mol% of C_1-symmetric Rh/Phebox complexes **3i** and **3j** (Figure 1) to afford the corresponding propargylic alcohols with greater than 99% *ee*. Because the acetate ligand on the Rh complex acted as an internal base, the reactions proceeded at 25 °C without any additives. An indanyl substituent on the oxazoline ligand was effective for obtaining high enantioselectivity and, in most cases, the C_1-symmetric complex gave better results than the C_2-symmetric complex. The electronic tuning of the Rh complex was achieved by introducing a nitro group at the *para* position to Rh and greatly improved both the reactivity and selectivity of the reaction. Moreover, the Rh complex had unique chemoselectivity; it selectively reacted with a α-ketoester over an aldehyde, thus allowing for the direct use of 4-ethynylbenzaldehyde as the nucleophile.

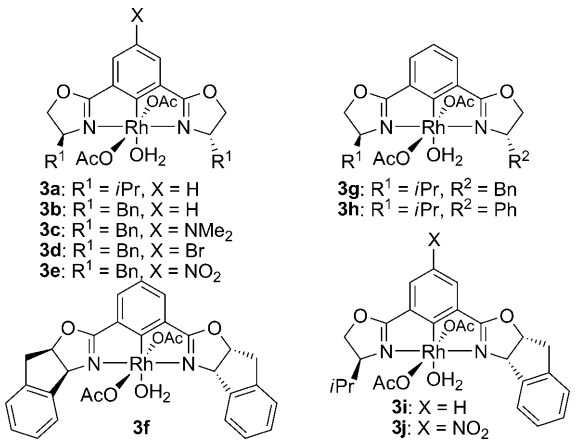

Figure 1. Structure of C_2- and C_1-symmetric Rh/Phebox complexes **3**. Bn = benzyl.

We began to develop an efficient catalytic asymmetric alkynylation of CF_3-substituted α-ketoester **1** because of the

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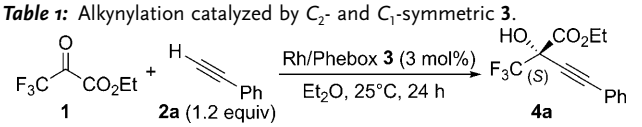
[**] This work was supported by a Grant-in-Aid for Science Research on Innovative Areas "Chemistry of Concerto Catalysis" (No. 10313123) and a Grant-in-Aid for Scientific Research (B) (21390003) from MEXT, CREST from JST, and the Takeda Science Foundation.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201100252.

increasing demand for CF_3-containing chiral compounds,[10p,12] such as the anti-HIV drug Efavirenz,[13] in pharmaceutical science. First, we screened various metal complexes such as Zn, Cu, Ag, and In complexes. Among the complexes initially tested, only the Rh/Phebox complex **3a**[14] promoted the reaction of **1** with phenylacetylene (**2a**; Table 1,

Table 1: Alkynylation catalyzed by C_2- and C_1-symmetric **3**.



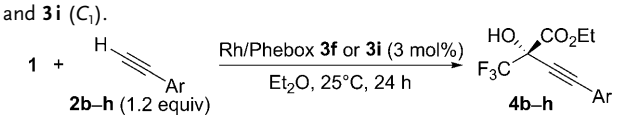
Entry	3 (C_2)	Yield [%][a]	*ee* [%][b]	Entry	3 (C_1)	Yield [%][a]	*ee* [%][b]
1	**3a**	35	88	4	**3g**	99	86
2	**3b**	87	83	5	**3h**	41	92
3	**3f**	94	91	6	**3i**	95	91

[a] Yield of the isolated product. [b] Determined by HPLC analysis.

entry 1).[15] Although the yield of product **4a** was modest (35%), the reaction proceeded at 25°C and the enantioselectivity was 88% *ee*.[16] Encouraged by this result, we examined the ligand effects of the catalyst. We recently reported that the trifluoroacetate-bridged tetranuclear zinc cluster $Zn_4(OCOCF_3)_6O$ efficiently catalyzed the direct conversion of esters, carboxylic acids, and nitriles into oxazoline.[17] Under these zinc-cluster-catalyzed conditions, carboxylic acids reacted much faster than nitriles or esters, thus allowing for easy access to a variety of C_1-symmetric bis(oxazoline) ligands, which contain different oxazoline moieties.[18,19] Therefore, we tested both C_2-symmetric Rh/Phebox complexes (**3a**, **3b**, and **3f**) and C_1-symmetric complexes (**3g–i**) for the alkynylation of **1** with **2a**. Although Rh complex **3h** gave the best enantioselectivity (92% *ee*; Table 1, entry 5), the Rh complexes that have indanyl substituents (**3f** and **3i**)[20] were the best in terms of both yield (up to 95%) and enantioselectivity (91% *ee*; Table 1, entries 3 and 6).

With catalysts **3f** and **3i** in hand, we investigated the scope and limitations of aryl-substituted alkynes **2b–h** (Table 2). The alkynylation using phenylacetylenes that contain electron-donating groups was smoothly catalyzed by the C_1-

Table 2: Alkynylation with aryl-substituted alkynes catalyzed by **3f** (C_2) and **3i** (C_1).

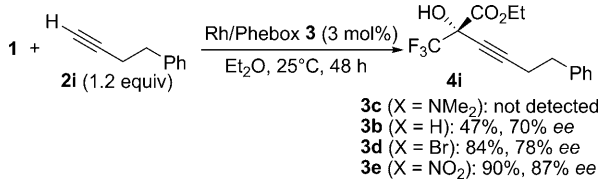


Entry	2	Ar	Using catalyst **3f** yield [%][a]	*ee* [%][b]	Using catalyst **3i** yield [%][a]	*ee* [%][b]
1	**2b**	4-MeC_6H_4	82	95	90	94
2	**2c**	3-MeC_6H_4	83	89	99	90
3	**2d**	2-MeC_6H_4	84	93	99	92
4	**2e**	4-$MeOC_6H_4$	78	80	88	90
5	**2f**	4-FC_6H_4	83	92	90	90
6	**2g**	4-BrC_6H_4	86	94	89	95
7	**2h**	4-$CF_3C_6H_4$	85	86	90	92

[a] Yield of the isolated product. [b] Determined by HPLC analysis.

symmetric Rh complex **3i** at room temperature to afford the products in high yield (up to 99%) and high enantioselectivity (up to 94% *ee*), while C_2-symmetric Rh complex **3f** was less effective (Table 2, entries 1–4). The Rh complex **3i** also gave slightly better results than **3f** in the alkylation of phenylacetylenes **2f–h**, which contain electron-withdrawing groups (Table 2, entries 5–7).

Alkynylation using alkyl-substituted alkynes, however, resulted in unsatisfactory results, even when the optimized catalyst **3i** was used.[15] For example, the reaction using the phenethyl-substituted acetylene **2i** gave only a 29% yield of the product, thus requiring the development of a more powerful catalyst. An attractive feature of the metal/Phebox complex is the ease of its electronic tuning by the introduction of an electron-donating or electron-withdrawing group at the *para* position to the metal.[14,21,22] To investigate the electronic effects of the Rh/Phebox catalyst, we synthesized dimethylamino-, bromo-, and nitro-substituted complexes **3c–e** and applied them to the alkynylation of **1** with **2i** (Scheme 1).



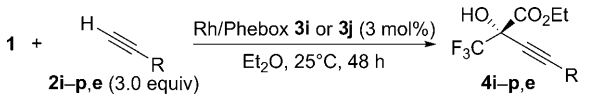
Scheme 1. Electronic tuning of Rh/Phebox complex **3**.

Although the introduction of the electron-donating dimethylamino group did not induce a reaction, the bromo- and nitro-substituted complexes **3d**[20] and **3e** remarkably improved both yield and enantioselectivity of the product **4i** compared with **3b** (Scheme 1), thus suggesting that the Lewis acidity of the Rh complex **3** is another important factor for catalytic activity and selectivity.

These results led us to examine the nitro-substituted C_1-symmetric Rh complex **3j** ($X = NO_2$) as the catalyst for the alkynylation of less-reactive substrates. As expected, the Rh-catalyst **3j** efficiently catalyzed the alkynylation of various alkyl-substituted acetylenes **2i–p** (Table 3). With all the tested substrates, **3j** ($X = NO_2$) gave much higher yield and/or enantiomeric excess than **3i** ($X = H$). For example, the enantioselectivity of the reaction with cyclopropylacetylene (**2l**) was improved from 29% *ee* to 74% *ee* (Table 3, entry 4). In addition, the use of catalyst **3j** successfully accelerated the reactions with **2m–o** (Table 3, entries 5–7). The obtained functionalized propargylic alcohols **4n–p** are of great interest because they can be easily converted into the corresponding terminal alkynes and propiolaldehyde derivatives. Catalyst **3j** was also effective for the reaction of aryl-substituted alkyne **2e**, thus affording product **4e** in 85% yield with >99% *ee* (Table 3, entry 9).

During the investigation of substrate scope,[23] we found that the present Rh catalysis has unique chemoselectivity. Aldehydes are generally much more reactive electrophiles than ketones. However, the alkynylation of benzaldehyde **5** was not promoted by Rh catalyst **3i**. We therefore performed

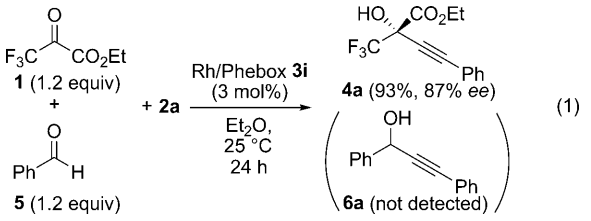
Table 3: Alkynylation with alkyl-substituted alkynes catalyzed by **3i** and **3j**.



Entry	2	R	Using catalyst **3i** yield [%][a]	*ee* [%][b]	Using catalyst **3j** yield [%][a]	*ee* [%][b]
1	**2i**	CH_2CH_2Ph	82	81	91	92
2	**2j**	*n*Pr	66	85	91	93
3	**2k**		85	87	93	96
4	**2l**		94	29	97	74
5	**2m**	*t*Bu	42	79	81	92
6	**2n**	TMS	52	82	72	84
7	**2o**		44	94	79	94
8	**2p**	$CH(OEt)_2$	68	83	61	86
9	**2e**	4-$MeOC_6H_4$	88	90[c]	85	>99

[a] Yield of the isolated product. [b] Determined by HPLC analysis. [c] Reaction time was 24 h. TMS = trimethylsilyl.

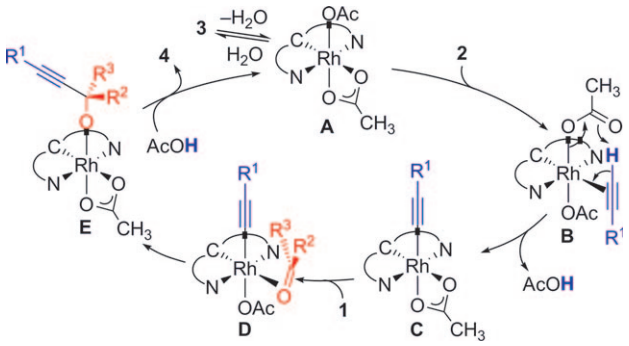
competition experiments using an equimolar mixture of ketoester **1** and aldehyde **5**, thus resulting in the exclusive formation of tertiary alcohol **4a** [Eq. (1)]. In contrast, other



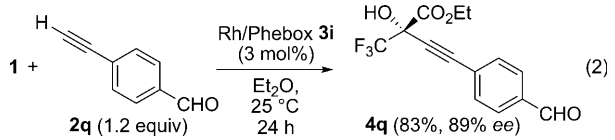
(1)

representative alkynylation conditions (lithium alkynylide, Zn catalyst, and In catalyst) led to only a nonselective or sluggish reaction.[15] Even though **1** is a rather reactive ketone, to the best of our knowledge, this is the first example of a chemoselective alkynylation of a ketone over a aldehyde. To demonstrate the usefulness of this chemoselectivity that is induced by the Rh/Phebox catalyst **3**, we attempted the direct use of 4-ethynylbenzaldehyde (**2q**) as the nucleophile [Eq. (2)]. Under the optimized reaction conditions, the Rh/Phebox complex **3i** smoothly catalyzed the alkynylation of **1** with **2q** to give the corresponding propargylic alcohol **4q** (83%, 89% *ee*), the synthesis of which generally requires a protection/deprotection process.[15]

To gain insight into the mechanism of this Rh catalysis, we performed the following experiments. Replacement of acetate ligand of **3** with a more electron-withdrawing ligand, such as trifluoroacetate, triflate, or chloride, severely retarded the reaction.[15] These data, taken together with the fact that the addition of an external base (Et_3N) did not affect either the yield or enantioselectivity, suggested that the acetate ligand on **3** acted as an internal base to efficiently deprotonate the coordinated terminal alkyne to form an Rh/alkynylide intermediate. Indeed, the formation of this Rh/alkynylide complex was confirmed by X-ray crystallographic analysis.[24] The linear relationship between the enantioselectivity of the chiral ligand and the extent of the asymmetric induction indicated the involvement of a monomeric active species.[15] In addition, crossover experiments suggested that a retro reaction of the alkynylation was not involved in the catalytic cycle.[15] Although the detailed reaction mechanism remains unclear, based on these results, we propose the bifunctional[25] catalytic cycle shown in Scheme 2, where the Rh center acts as a π acid[26] and/or Lewis acid to activate the alkyne (**A**→**B**) and the ketone (**D**→**E**), and the acetate moiety on the Rh acts as a Brønsted base to deprotonate the terminal alkyne in an intramolecular fashion (**B**→**C**).



Scheme 2. Proposed catalytic cycle of **3**-catalyzed alkynylation.



(2)

In summary, we have developed a catalytic asymmetric alkynylation of α-ketoesters with aryl- and alkyl-substituted alkynes that is promoted by 3 mol% of the C_1-symmetric Rh/Phebox complexes at room temperature. Introduction of an electron-withdrawing nitro group at the *para* position to Rh greatly improved both the reactivity and selectivity of the reaction. The present catalytic system has a unique chemoselectivity, thus resulting in the α-ketoester being alkynylated in preference to an aldehyde. Investigations into the application of this method to the synthesis of bioactive compounds are ongoing.

Experimental Section

Rh/Phebox complex (0.0060 mmol, 3.0 mol%), ethyl trifluoropyruvate (**1**, 34.0 mg, 0.20 mmol), and **2** (0.24 mmol, 1.2 equiv) in Et_2O (2.0 mL) were stirred at 25 °C for 24 h under an argon atmosphere. The resulting mixture was concentrated in vacuo and purified by flash column chromatography on silica gel (eluent: ethyl acetate/hexanes (1:8)) to give the desired product **4**.

Received: January 12, 2011
Published online: May 30, 2011

Keywords: alkynylation · asymmetric catalysis · chemoselectivity · ketones · rhodium

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[15] For details, see the Supporting Information.

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