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Highly enantioselective spiro cyclization of 1,6-enynes catalyzed by cationic skewphos rhodium(I) complex†

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Received (in Cambridge, UK) 5th September 2003, Accepted 14th October 2003
First published as an Advance Article on the web 7th November 2003

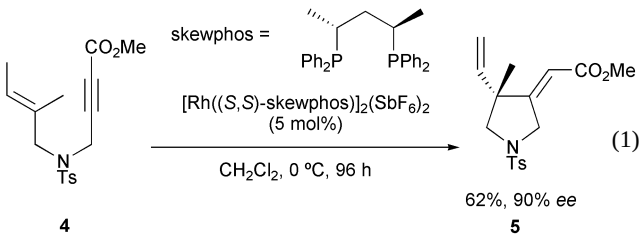
A cationic rhodium(I) complex having a skewphos ligand is shown to be a highly enantioselective catalyst for asymmetric carbocyclization of 1,6-enynes with tri-substituted olefins to control quaternary stereogenic centers of spiro-rings.

Transition metal catalysed ene-type cyclization of 1,6-enynes[1,2,3] are useful methods particularly for 5-membered rings. However, precedent examples for enantioselective catalysis with chiral metal complexes are limited to palladium[4,5] and rhodium[6,7] complexes, despite its synthetic potential leading not only to carbocycles but also to heterocycles.[8] Recently, X. Zhang has reported excellent examples[9] that a chiral rhodium complex is advantageous in terms of the facile cyclization even at room temperature but only applicable to disubstituted *cis*-olefin substrates. Herein, we report efficient catalysis of ene-type cyclization including tri-substituted 1,6-enynes by cationic chiral rhodium(I) complexes[10] bearing a skewphos ligand.[11] The chirally dynamic (*tropos*: turn in Greek)[12] skewphos provides a deep insight into the key transition states for C–C bond formation.

First, the feasibility of the ene-type carbocyclization was investigated for a tri-substituted olefinic ether substrate **1** using 5 mol% of cationic Rh(I) catalyst including a variety of achiral bidentate PP-ligands in dichloromethane at room temperature (Table 1). Since the cationic Rh(I)(PP-ligand) dimer complexes[11,13] are usually unstable to isolation or are difficult to store in solution for any length of time even at low temperature, "*in-situ* preparation"[14] is adopted in our reactions. Interestingly, the normal ene-type cyclization proceeds even with such a sterically congested tri-substituted olefinic substrate, but along with the unexpectedly isomerised *endo*-cyclic secondary products **3** with dppe (1,2-bis(diphenylphosphino)ethane) (entry 1). By contrast, dppp (1,3-bis(diphenylphosphino)propane) and dppb (1,4-bis(diphenylphosphino)-butane) gave the desired ene-type cyclization products **2** with high regioselectivities (entries 2 and 3).

Next we examined the chiral PP-ligands such as (*S*)-BINAP and (*S*,*S*)-skewphos ((2*S*,4*S*)-2,4-bis(diphenylphosphino)pentane, (*S*,*S*)-BDPP)[13] corresponding to dppp and dppb skeletons, respectively. The key to the success in increasing the enantioselectivities and olefinic regioselectivities in carbocyclization is the use of skewphos rather than BINAP (entry 4) to give 93% *ee* and 90% olefinic regioselectivities at room temperature (entry 5). Even at 0 °C, reaction with (*S*,*S*)-skewphos proceeded slowly, and moreover olefinic regioselectivity increased up to 98% with maintaining chemical yield and enantioselectivity of the major product **2** (entry 6).

Furthermore, catalytic asymmetric cyclization of amide substrate **4** using Rh(I)/(*S*,*S*)-skewphos complex proceeded in moderate yield but without olefin migration, to afford **5** involving quaternary carbon center as a sole product (Eqn. 1).



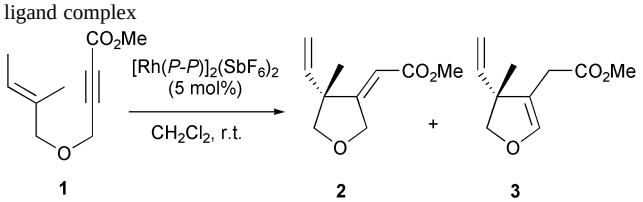
(1)

4 **5**

Encouraged by these interesting results among tri-substituted substrates, we next tried the spiro-cyclizations of ether compounds **6** catalyzed by chiral cationic Rh(I)/(*S*,*S*)-skewphos complex (Table 2). Cyclization of **6a** with 6-membered ring was executed at room temperature for 46 hours to give **7a** in 53% yield and 88% *ee*, together with olefin-migration product **8a** with high enantiomeric excess (97% *ee*).[15]

The reactivity increased dramatically at 80 °C and the cyclization of **6a** completed within only 40 minutes but **8a** was obtained in high enantioselectivity (44%, 91% *ee*) (entry 2). For **6b** involving 8-membered medium ring, the major product was **8b** under either

Table 1 Ene-type cyclizations of 1,6-enynes catalyzed by cationic Rh(I)/PP-ligand complex



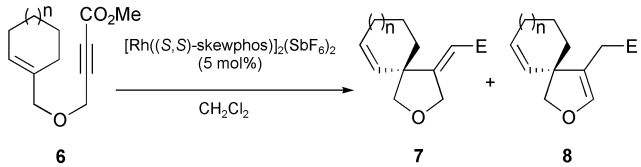
1 **2** **3**

Entry	PP-ligand	Reaction time/h	Yield (%) **2**[a]	Yield (%) **3**[a]
1	dppe	7	47 (—)	33 (—)
2	dppp	6	84 (—)	2 (—)
3[b]	dppb	4	66 (—)	13 (—)
4	(*S*)-BINAP	3	90 (28, *S*)	10 (18, *S*)
5	**(*S*, *S*)-skewphos**	7	59 (**93**, *R*)	6 (> **95**,*R*)
6[b]	**(*S*, *S*)-skewphos**	84	59 (**94**, *R*)	1 (> **95**,*R*)

[a] Ee (%) in parentheses. [b] Temperature is 0 °C.

† Electronic supplementary information (ESI) available: typical experimental procedure and spectral data for **1–10**. See http://www.rsc.org/suppdata/cc/b3/b310789b/

Table 2 Enantioselective spiro cyclization catalyzed by a cationic (*S*,*S*)-skewphos rhodium(I) complex



6 **7** **8**

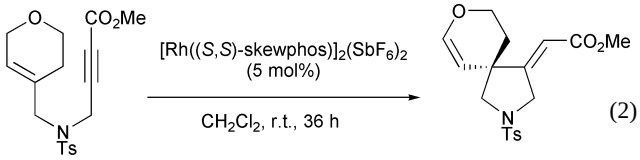
Entry	Substrate (*n*)	*T* [°C]	Reaction time	Yield (%) **7**[a]	Yield (%) **8**[a]
1	**6a** (1)	r.t.	46 h	53 (88)	16 (97)
2	**6a** (1)	80	40 min	4 (67)	44 (91)
3	**6b** (3)	80	40 min	6 (79)	55 (79)
4	**6b** (3)	40	17 h	12 (88)	51 (88)

[a] Ee (%) in parentheses.

DOI: 10.1039/b310789b

40 °C or 80 °C conditions, although the enantioselectivity was high (88% *ee* and 79%*ee*, respectively) (entry 3 and 4).

To increase the synthetic usefulness, spiro-cyclization[16] of pyran amide compound **9** was executed (Eqn. 2). Spiro cyclization proceeds smoothly at room temperature to afford the desired spiro amide-pyran **10** with extremely high enantioselectivity of 94% *ee* without accompanying any olefin migration.



(2)

9 **10**

It should be noted that the transition states for C–C bond formation[9c] indicate the chirally dynamic (*tropos*) nature of the skewphos ligand. Skewphos is known to have both chair and skew forms and these forms exist in equilibrium with each other[17] (Fig. 1). As its name shows, skewphos is stable in the favourable skew conformation (λ- over δ-skew forms).[16,17] In fact, due to their uncontrollable nature, examples of asymmetric catalysis using skewphos analogues are very limited although some chiral skewphos analogues have been devised.[18–20] Undoubtedly, BINAP has a rigid (*atropos*: not turn in Greek)[12] binaphthyl skeleton and cannot easily epimerize. (*S*)-Enriched cyclized product **2** was obtained by enantiopure and *atropos* (*S*)-BINAP,[20,21] which has (I,III)-equatorial phenyl groups in the Rh-quadrant (Table 1, entry 4). On the other hand, we obtained (*R*)-enriched cyclized product **2** by (*S*,*S*)-skewphos, in sharp contrast to the (*R*)-product obtained with (*S*)-BINAP (Table 1, entries 5 and 6). In our ene-type cyclization, (*S*,*S*)-skewphos should possess the less stable δ-skew form in (I,III)-equatorial conformation as does (*S*)-BINAP. Therefore it is indicated that our cationic Rh(I)-catalyzed ene-type cyclizations should proceed *via* the less favourable λ-skew form. In the λ-skew form, the (II,IV)-equatorial phenyl groups are inclined a little from the horizontal because of the repulsion between two axial-Me groups of skewphos and these Ph groups. In quadrants II and IV in the δ-skew form, a vacant space is available for the bulky alkyl group of the substrate, leading to (*R*)-enriched product **2** without conspicuous repulsions.

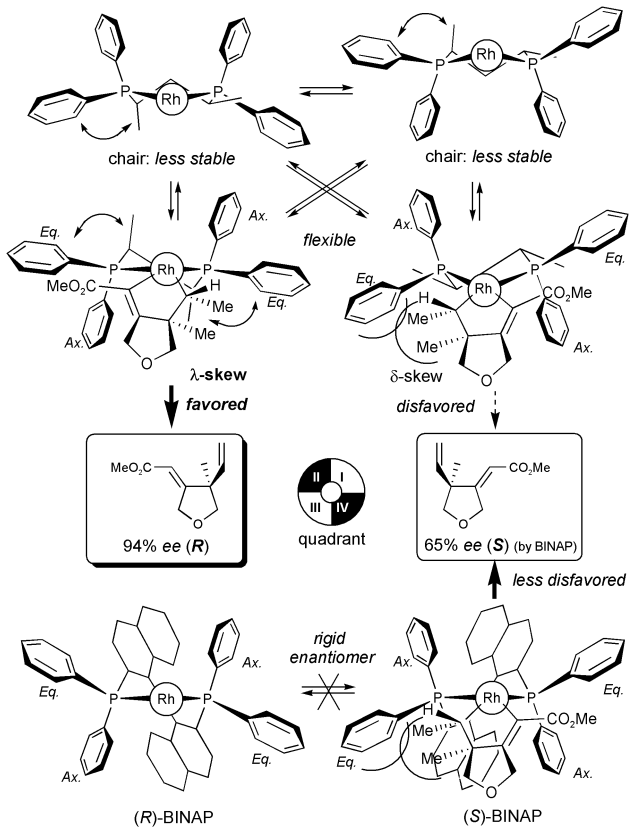


Fig. 1 Flexible skew-conformation of skewphos *vs.* rigid BINAP.

In summary, we have developed highly enantioselective spiro cyclization of 1,6-enynes with tri-substituted olefin catalysed by cationic skewphos rhodium(I) complex. This is the first example of spiro-constructions by Rh(I) catalysis *via* ene-type cyclization. Further mechanistic analyses and crystallization of cationic Rh(I) complexes for X-ray analyses are now under way.

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