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Asymmetric Binary-Acid Catalysis with $InBr_3$ in the Inverse-Electron-Demanding Hetero-Diels–Alder Reaction of Mono- and Bis-Substituted Cyclopentadienes: Remote Fluoro-Effect on Stereocontrol

Jian Lv, Long Zhang, Shenshen Hu, Jin-Pei Cheng, and Sanzhong Luo*[a]

The inverse-electron-demanding hetero-Diels–Alder reaction of α,β-unsaturated-carbonyl compounds and alkenes is one of the versatile approaches for the synthesis of dihydropyran derivatives.[1,2] Currently, several catalytic enantioselective processes have been developed,[3] however, with one single exception: cyclopentadiene, CP; this reaction has been limited to electron-rich alkenes such as enol ethers[3a,b] and enamines.[4] To enable the reaction with less reactive alkenes would significantly expand the synthetic utility. In this regard, 1,3-dienes, particularly cyclopentadienes, are appealing substrates due to their wide utilization as building blocks in organic synthesis. Apart from the issues of stereoselective control, the reaction of CP has the additional periselectivity problem in differentiating the two bifurcating Diels–Alder and hetero-Diels–Alder pathways. It even becomes more challenging in the context with substituted CPs in which serious issues of regioselective control are raised, a situation that arises from, on one hand, the labile nature of substituents on CP ring due to the facile [1,5]-sigmatropic rearrangement and, on the other hand, the difficulties with separations of CP regioisomers as well as their regioisomeric adducts. Recently, Yamamoto reported the first example of regio- and enantioselective Diels–Alder reactions of mono-substituted CPs.[5] There is strikingly no report on the use of bis-substituted CPs in asymmetric Diels–Alder and hetero-Diels–Alder reactions. We herein present the first catalytic regio-, peri- and stereoselective hetero-Diels–Alder reaction of mono- and bis-substituted CPs. This reaction is made possible by an asymmetric binary-acid strategy that synergistically integrates a chiral Brønsted acid and a Lewis acid, leading to mutually enhanced acidity with concomitant generation of multiacidic centers for synergistic catalysis.[6,7] Taking advantage of this intriguing feature as well as the combinatorial flexibility, we examined this binary-acid catalysis in the inverse-electron-demanding hetero-Diels–Alder reactions of CPs.

Our investigation started with a model cycloaddition between cyclopentadiene **2a** and β,γ-unsaturated-α-ketoester **3a**, for which the parent chiral phosphoric acid **1a** is totally inert (Table 1, entry 1). To our delight, the combined use of **1a** with a Lewis acid led to an active reaction with marked enantioselectivity and the hetero-Diels–Alder pathways are generally favored under these conditions. A survey of different Lewis acids was then followed and the best results were again obtained with $InBr_3$ in terms of both reactivity and stereoselectivity (Table 1, entry 7), whereas other Lewis acids resulted in either low activity or poor enantioselectivity (Table 1, entries 2–8).

The impact of the ratio of two acids was also examined. Whereas the activity was maintained at a similar level by increasing the ratio of **1a**/$InBr_3$ from 1:1 to 2:1, the enantioselectivity was considerably improved when using a higher ratio of **1a**/$InBr_3$ (2:1) (Table 1, entry 7 vs. 9). Further increasing the ratio to 3:1 did not lead to further improvement in activity (Table 1, entry 10). ESI-MS studies indicated that when the ratio was increased from 1:1 to 2:1 or higher, the metal would completely assemble with the free phosphoric acid; no free indium species is detected under a higher ratio (>2:1).[6b] Both the 2:1 and 1:1 complex are present in solution together with free phosphoric acid regardless of the molar ratio of **1a**/$InBr_3$.[6b] These results indicate that a free phosphoric acid such as **1a** performs well as a chiral ligand in non-protic media, albeit with weak coordinating properties; the catalysis with free $InBr_3$ would slightly favor the DA pathway rather than HDA pathway (Table 1, entry 7 vs. 8). In addition, the free phosphoric acid **1a** was found to be superior to its alkaline salts such as **1c** and **1d** (with reversed peri-selectivity, Table 1, entries 12 and 13) or pyridinium salt **1b** (no activity, Table 1, entry 11) in terms of both activity and selectivity. These observations, together with the dramatic effect of metal Lewis acids on both activity and stereoselectivity (e.g., Table 1, entry 7 vs. entries 3 and 4), highlight the synergistic combinations of free phosphoric acid and Lewis acid for effective catalysis, and the role of free phosphoric acid (e.g., **1a**) as a dual ligand and acid is thus verified.

With the Lewis acid $InBr_3$, we next set out to further improve the stereoselectivity by examining different free phosphoric acids. Interestingly, steric tuning, a strategy widely

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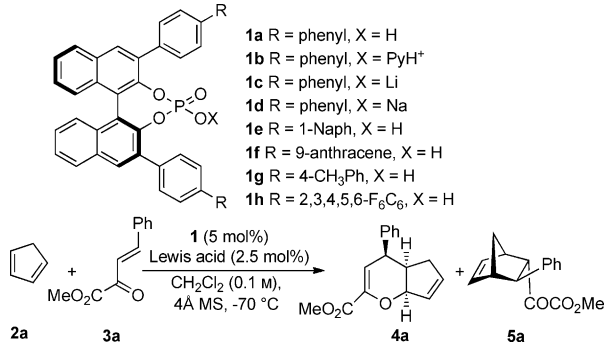
Table 1. Selected screening and optimization results.[a]



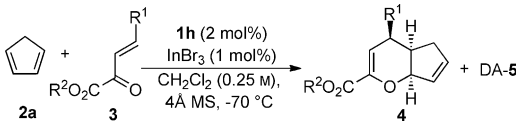
Entry	**1**/Lewis acid	Yield [%][b]	**4a**/**5a**	*ee*/**4a** [%][c]	*ee*/**5a** [%][c]/d.r.	Entry	**1**/Lewis acid	Yield [%][b]	**4a**/**5a**	*ee*/**4a** [%][c]	*ee*/**5a** [%][c]/d.r.
1	**1a**/none	NR[d]	–	–	–	10[f]	**1a**/$InBr_3$	99	72/28	80	80/90:10
2	**1a**/$Mg(OTf)_2$	28	67/33	28	28/90:10	11	**1b**/$InBr_3$	NR[d]	–	–	–
3	**1a**/$Sc(OTf)_3$	99	79/21	−79	−79/90:10	12	**1c**/$InBr_3$	99	25/75	80	82/90:10
4	**1a**/$Cu(OTf)_2$	51	70/30	−39	−40/90:10	13	**1d**/$InBr_3$	99	43/57	76	76/90:10
5	**1a**/$Bi(OTf)_3$	40	68/32	30	30/85:15	14	**1e**/$InBr_3$	99	75/25	89	89/90:10
6	**1a**/$In(OTf)_3$	99	72/28	57	57/90:10	15	**1f**/$InBr_3$	52	75/25	4	5/90:10
7	**1a**/$InBr_3$	99	72/28	80	80/90:10	16	**1g**/$InBr_3$	99	71/29	81	85/90:10
8	None/$InBr_3$	99	40/60	–	–	17	**1h**/$InBr_3$	99	81/19	99	98/99:1
9[e]	**1a**/$InBr_3$	99	70/30	56	56/90:10	**18**[g]	**1h/InBr$_3$**	**99**	**81/19**	**99**	**98/98:2**

[a] General conditions: **2a** (0.625 mmol), **3a** (0.125 mmol), **1** (5 mol%), Lewis acid (2.5 mol%), and 4Å molecular sieves (MS) (20 mg) at −70°C in CH_2Cl_2, 4 h; except for entries 1 and 2, 4–6, and 8, 24 h and for entry 18, 12 h. [b] Isolated product yield. [c] Enantioselectivities were determined by HPLC analysis. [d] NR: No reaction. [e] **1a** (2.5 mol%). [f] **1a** (7.5 mol%). [g] **1h** (2 mol%) and $InBr_3$ (1 mol%) in CH_2Cl_2 (0.5 mL) for 12 h.

applied in the catalysis with phosphoric acids,[8] worked against us. For example, though moderate improvement of stereoselectivity could be obtained by switching the remote phenyl ring to a naphthyl group (Table 1, entry 7 vs. 14), the incorporation of a larger 9-anthracyl moiety led to dramatic depletion of both activity and stereoselectivity (Table 1, entry 15, for more examples see the Supporting Information), suggesting that steric interaction is not the determining factor for stereocontrol in our binary-acid catalysis. After trial and error, it was found that stereoselectivity enhancement could only be achieved by remote substituent tuning of the 4′-phenyl moiety, which turns out to be the essential structural unit for stereocontrol (Table 1, entries 14–17, see below for a discussion). An optimal phosphoric acid bearing a pentafluorophenyl group, PentaF-**1h**, was eventually reached through electronic tuning of the remote phenyl group. This binary-acid catalyst PentaF-**1h**/$InBr_3$ demonstrated good periselectivity (**4a**/**5a** = 81:19), so far the best periselectivity that has been achieved for a HDA pathway,[9] and excellent stereoselectivity (99% enantiomeric excess (*ee*) for **4a**, *endo*/*exo* = 99:1, 98% *ee* for **5a**; Table 1, entry 17). In addition, the catalyst loading can be reduced from 2.5 mol% to 1 mol% while maintaining a similar performance (Table 1, entry 18).

The catalytic scope of the obtained optimal binary-acid PentaF-**1h**/$InBr_3$ was next explored in the reactions of cyclopentadienes, with a focus on those of mono- and bis-substituted CPs. As shown in Table 2, a variety of β,γ- unsaturated α-ketoesters can be applied in the reactions with cyclopentadiene to give the desired HDA products **4a–i** and DA products **5a–i** in good yields (**4/5** up to 87:13) and excellent enantioselectivity for both **4** (>98% *ee*) and **5** (95–99% *ee*, >96:4 *endo*/*exo*).

Table 2. DA and HDA reaction between CP **2** and β,γ-unsaturated-α-ketoesters **3**.[a]

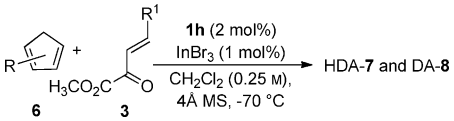


Entry	R_1	R_2	Yield [%][b]	**4**/**5**	*ee*/**4** [%][c]	*ee*/**5** [%][c]/d.r.
a	Ph	Me	99	81/19	99	98/98:2
b	4-ClC_6H_4	Me	99	81/19	98	98/99:1
c	3,4-$Cl_2C_6H_3$	Me	99	78/22	99	98/98:2
d	2-FC_6H_4	Me	99	83/17	98	98/96:4
e	4-MeC_6H_4	Me	99	81/19	99	98/97:3
f	4-$MeOC_6H_4$	Me	88	87/13	99	99/99:1
g	4-PhC_6H_4	Me	99	80/20	>99	>99/99:1
h	Ph	*i*Pr	99	80/20	>99	95/98:2
i	3,4-$Cl_2C_6H_3$	Et	99	79/21	99	99/98:2

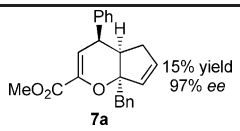
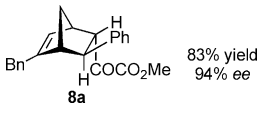
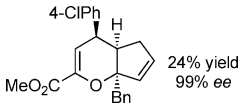
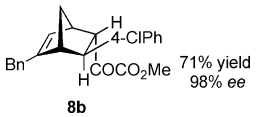
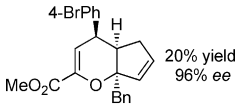
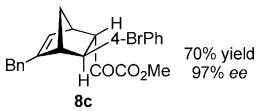
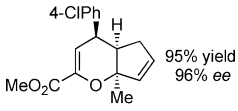
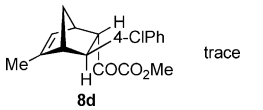
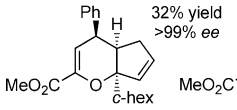
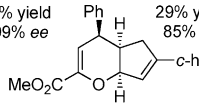
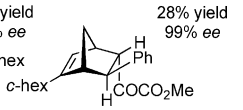
[a] General conditions: **2** (0.625 mmol), **3** (0.125 mmol), **1h** (2 mol%), $InBr_3$ (1.0 mol%) and 4Å MS (20 mg) at −70°C in CH_2Cl_2, 12 h; for entries e–g, 48 h. [b] Isolated product yield. [c] Enantioselectivities were determined by HPLC analysis.

Experiments were then conducted to explore the reactions with substituted CPs in the presence of **1h**/$InBr_3$. The inseparable regioisomeric mixtures of substituted CPs (two regioisomers for mono-substituted CPs and more than four isomers for bis-substituted CPs) were directly employed (Table 3 and Table 4). Remarkably, the reactions occur regioselectively with one isomer among their respective mix-

Table 3. DA and HDA reaction between mono-substituted cyclopentadienes **6** and β,γ-unsaturated α-ketoesters **3**.[a]



6 3

Entry	Product	
a	 15% yield, 97% *ee* **7a**	 83% yield, 94% *ee* **8a**
b	 24% yield, 99% *ee* **7b**	 71% yield, 98% *ee* **8b**
c	 20% yield, 96% *ee* **7c**	 70% yield, 97% *ee* **8c**
d	 95% yield, 96% *ee* **7d**	 trace **8d**
e	 32% yield, >99% *ee* **7e**  29% yield, 85% *ee* **7e'**  28% yield, 99% *ee* **8e**	

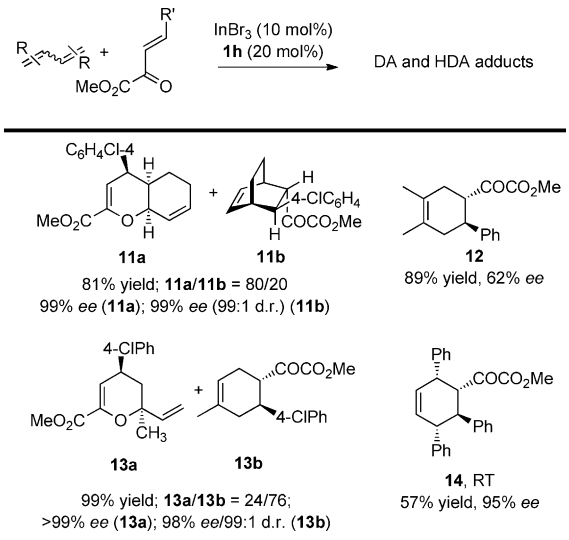
[a] General conditions: **6** (0.625 mmol), **3** (0.125 mmol), **1h** (2 mol%), $InBr_3$ (1.0 mol%) and 4Å M.S. (20 mg) at −70 °C in CH_2Cl_2, 1 h.

tures of regioisomers. In the case of mono-substituted CPs, 3-substituted CPs are generally preferred except in one case (with a steric demanding cyclohexyl-substituted CP (Table 3, entry e)) in which the reactions favored either HDA products or DA products depending on the substitution (Table 3). For bis-substituted CPs, the reactions proceeded exclusively with 1,3-bis-subsituted CPs to give hetero-Diels–Alder adducts as single stereoisomers and substituents including benzyl, alkyl, and allyl groups are well accommodated in the reactions (Table 4).[10] In both cases, the corresponding adducts were obtained in high yields with excellent diastereoselectivity and enantioselectivity (Tables 3 and 4).[11] Heteroaromatic and alkyl-substituted ketoesters are equally applied to the current reactions, though the latter reaction is less selective (Table 4, entries 10 and 11). To the best of our knowledge, the current results represent the first examples on using substituted CPs in hetero-Diels–Alder reactions.

Other 1,3-dienes have also been examined in the current reactions (Scheme 1). Accordingly, cyclohexa-1,3-diene and acyclic 1,3-dienes such as isoprene and 2,3-dimethylbuta-1,3-diene can be applied to give DA or HDA adducts in high yields and with excellent enantioselectivity. Notably, *trans*, *trans*-1,4- diphenyl-1,3-butadiene is also a workable substrate, affording a single cyclohexane product **14** bearing four consecutive carbon stereogenic centers with excellent enantioselectivity (Scheme 1).

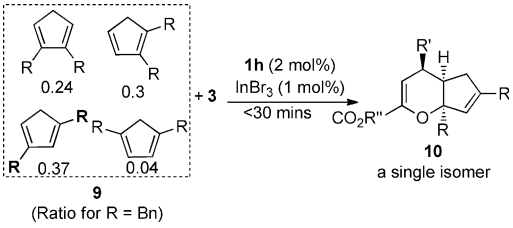
In an effort to unveil the origin of the unexpected remote substituent effect on stereocontrol (Table 1), a systematic substituent mapping has been carried out on the far 4′-phenyl moiety of chiral phosphoric acid **1** (Table 5). A survey of the data in Table 5 revealed several interesting observations: 1) there seems no uniform substituent trend since the obtained stereoselectivity do not correlate well with any single substituent parameter such as σ_p or σ_m, polarizability, surface area, quadrupole moment and dipole moment (see the Supporting Information for details); instead 2) substituent effect on stereocontrol is found to be highly position sensitive and a significantly beneficial stereoeffect is observed with *ortho*-substitution on the remote 4′-phenyl ring (Table 5, entry 3 vs. 2; entry 8 vs. entries 6 and 7), and 3) dramatic remote fluoro effect on stereocontrol is also noted and a single *ortho*-fluoro atom (see compound **1n**) is suffice to provide comparable stereocontrol with that of the optimal PentaF-**1h** (Table 1, entries 8 vs. 9, see the Supporting Information for more substrates test with **1n**),[12] indicating a distinctive stereocontrol mode that is undisclosed with chiral phosphoric acid catalysis.[5a,13]

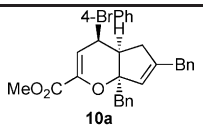
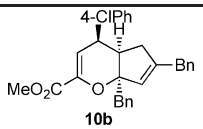
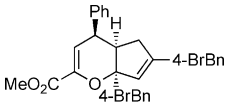
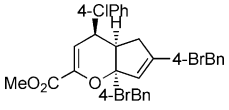
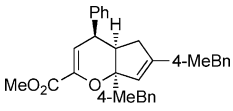
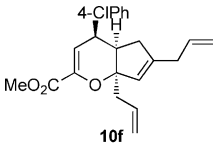
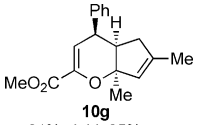
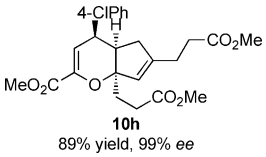
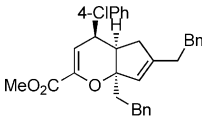
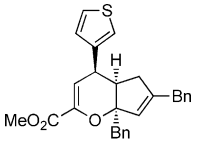
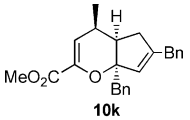
Based on the determined absolute configurations of (*4S,4aR*, *7aS*)-**4a** and (*2S,3R*)-**5a**, a tentative transition state[14] (consistent with Houk's model),[15] was proposed to account for the regio- and stereoselectivity (Figure 1). Accordingly, the reactions occur through bidentate activation of an α-ketoester by the catalytic active complex formed from chiral phosphoric acid (e.g., **1h** or **1n** and $InBr_3$ (1:1)).[16] Approach of CP from the



Scheme 1. The reactions with other 1,3-dienes.

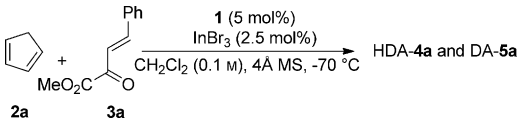
Table 4. DA and HDA reaction between mono-substituted cyclopentadienes **6** and β,γ-unsaturated α-ketoesters **3**.[a]

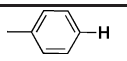
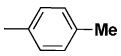
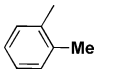
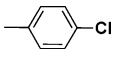
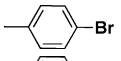
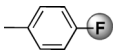
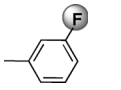
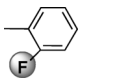
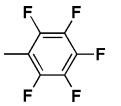


Entry		Entry	
1	 **10a** 90% yield, 97% *ee*	2	 **10b** 99% yield, >99% *ee*
3	 **10c** 92% yield, 97% *ee*	4	 **10d** 93% yield, 95% *ee*
5	 **10e** 85% yield, 94% *ee*	6	 **10f** 87% yield, >99% *ee*
7	 **10g** 91% yield, 95% *ee*	8	 **10h** 89% yield, 99% *ee*
9	 **10i** 87% yield, 98% *ee*	10	 **10j** 90% yield, 96% *ee*
11	 **10k** 86% yield, 53% *ee*		

[a] General conditions: **9** (0.625 mmol), **3** (0.125 mmol), **1h** (2 mol%), $InBr_3$ (1.0 mol%) and 4Å M.S. (20 mg) at −70 °C in CH_2Cl_2, 1 h.

Table 5. Remote substituent effect of chiral phosphoric acid.[a]



Entry		R	Yield [%]	**4a/5a**	*ee* **4a** [%]	*ee* **5a** [%]
1	**1a**		99	72/28	80	80 (90:10)
2	**1g**		99	71/29	81	85 (90:10)
3	**1i**		89	75/25	93	92 (92:8)
4	**1j**		90	55/45	79	94 (87:13)
5	**1k**		10	55/45	78	69 (80:20)
6	**1l**		98	70/30	86	87 (90:10)
7	**1m**		99	60/40	91	91 (87:13)
8	**1n**		**99**	**75/25**	**98**	**96 (94:6)**
9	**1h**		**99**	**81/19**	**99**	**99 (98:2)**

[a] General conditions: **2a** (0.625 mmol), **3a** (0.125 mmol), **1** (5.0 mol%), Lewis acid (2.5 mol%) and 4Å M.S. (20 mg) at −70 °C in CH_2Cl_2 for 4 h.

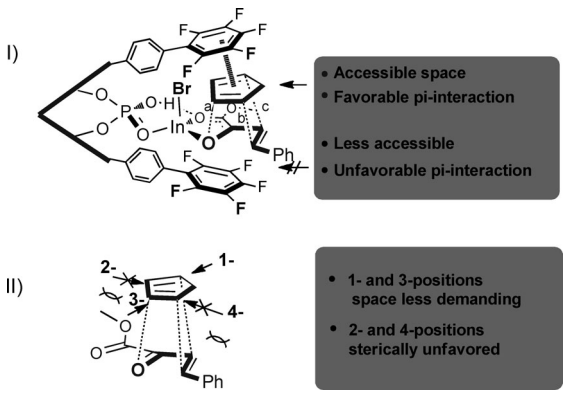


Figure 1. Proposed transition-state model for the stereocontrol (I) and regioselectivity control/substitution bias (II).

more accessible upper space by the aid of attractive π-interactions between fluorobenzene and CP and subsequent [a, b]- and [b, c]-*endo* additions lead to the HDA and DA adduct, respectively (Figure 1, I). Recently, single *ortho*-fluoro substitution has been shown to contribute significantly in aromatic stacking of a RNA-protein complex[17] and this precedent together with the well-known propensity of the pentafluorophenyl ring to participating in π–π stacking,[18] are supportive of an attractive π–π interaction with CPs for highly effective stereocontrol in our binary-acid catalyst.[19] The observed substituent bias as well as the obtained regioselectivity can be explained by considering the intrinsic steric effect on the 2- and 4-positions of CP ring in the proposed *endo*-transition state as a result of maximum orbital overlap requirement in the typical HDA pathway (Figure 1, II).[15]

In conclusion, we have developed the first peri-, regio- and enantioselective HDA reaction of mono- and bis-substituted cyclopentadienes catalyzed by a unique binary-acid **1h**/$InBr_3$. A salient feature of the current reactions is ascribed to the identification of an extremely active binary-acid catalyst **1n** or **1h**/$InBr_3$ that enables unprecedentedly

the reactions of substituted CPs and acyclic 1,3-dienes in good yields and with high enantioselectivity. In addition, we also disclose dramatic remote substituent effect, particularly the *ortho*-fluoro effect, on stereocontrol likely through π-interaction between fluorinated benzene ring and 1,3-dienes. This distinctive stereocontrol mode has not been reported in the catalysis with chiral phosphoric acid. Further work to elucidate the nature of this fluoro-effect is currently underway in our laboratory.

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Keywords: asymmetric catalysis · fluorine · hetero-Diels–Alder reaction · indium bromide · substituted cyclopentadienes · regioselectivity

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[9] For comparison, Ref. [3e] and [3j] reported periselectivity 66 :34 and 60: 40 favoring **4a**, respectively.

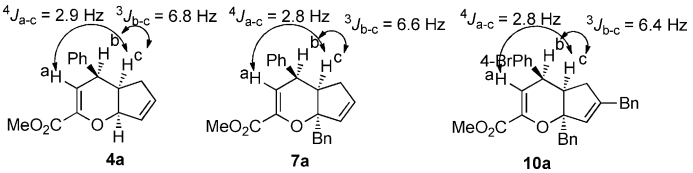
[10] As monitored by NMR and TCL, the reaction of **9h** and **9i** are slightly slower than other bis-substituted CPs. The reaction time was set at 30 min for the convenience of manipulation.

[11] A larger scale (1 mmol) reaction has also been tried to give the desired product **10b** (0.42 g, 90 % yield) with > 99 % *ee*.

[12] **1n** also performs comparably in the reactions with other substrates.

[13] For examples of the fluoro-effect on stereocontrol, see: a) S.-s. Jew, M.-S. Yoo, B.-S. Jeong, I. Y. Park, H.-g. Park, *Org. Lett.* **2002**, *4*, 4245–4248; b) T. Ooi, M. Takeuchi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.* **2000**, *122*, 5228–5229; c) K. Ishihara, D. Nakashima, Y. Hiraiwa, H. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 24–25.

[14] The relative configurations of **7** and **10** were established by ^{1}H NMR analysis according to Ref. [3e], [3f] and A. Martel, S. Leconte, G. Dujardin, E. Brown, V. Maisonneuve, R. Retoux, *Eur. J. Org. Chem.* **2002**, 514: The lower $^3J_{b-c}$ coupling constants and the existence of a ^4J coupling between the vinylic proton ^{a}H and ^{c}H strongly suggests a pseudo-equatorial position for ^{c}H, which rules out a *trans*-ring junction and thus implies a normal *endo* cycloaddition. The absolute configuration of **4a** was determined by comparison of optical rotation with the reported one ($[\alpha]_D^{25} = +191.1$ ($c = 1.3$, $CHCl_3$) (reported in Ref. [3e]: $[\alpha]_D^{25} = -226.5$ ($c = 1.2$, $CHCl_3$)). By assuming similar transition states, absolute configurations of **7a** and **10a** were assigned by analogy.



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[16] The product *ee* value was found to correlate linearly with the catalyst *ee* value, indicating that a higher ligand/metal complex is unlikely to be the catalytically active species. In addition, the fact that chiral phosphoric acid tends to aggregate as a racemic complex (1:1 *R/S* complex, see: N. Li, X.-H. Chen, S.-M. Zhou, S.-W. Luo, J. Song, L. Ren, L.-Z. Gong, *Angew. Chem.* **2010**, *122*, 6522; *Angew. Chem. Int. Ed.* **2010**, *49*, 6378) as well as our observation that heterocomplex (*R*)-**1h**-In- (*S*)-**1a** is a major species in the solution of *S*-**1a**, *R*-**1h** and $InBr_3$ (1:1:1 molar ratio) as determined by ESI-MS further exclude such a possibility. Therefore, a 1:1 complex is invoked to be the active catalytic species in the current reactions. The role of the extra chiral phosphoric acid employed is most likely to deplete any free indium species in solution that may lead to background reactions.

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[19] The *ortho*-F atom may also interact with the metal center, contributing to the effective catalysis. This possibility as well as some hydrogen-bonding effect of the *ortho*-F atom cannot be excluded presently. For a relevant example, see: S. M. Yu, S. Mecking, *J. Am. Chem. Soc.* **2008**, *130*, 13204–13205.

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