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Enantioselective Synthesis of Anti Homoallylic Alcohols from Terminal Alkynes and Aldehydes Based on Concomitant Use of a Cationic Iridium Complex and a Chiral Phosphoric Acid

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Supporting Information

ABSTRACT: We report a highly diastereo- and enantioselective synthesis of anti homoallylic alcohols from terminal alkynes via (*E*)-1-alkenylboronates based upon two catalytic reactions: a cationic iridium complex-catalyzed olefin transposition of (*E*)-1-alkenylboronates and a chiral phosphoric acid-catalyzed allylation reaction of aldehydes.

Stereocontrolled C−C bond formation in acyclic systems bearing multiple stereocenters is one of the most critical issues in organic synthesis. Allylation of carbonyl compounds with allylmetal reagents provides a reliable method for the enantioselective synthesis of homoallylic alcohols,[1,2] so it is often used for the asymmetric synthesis of polyketide natural products.[3] Thus, the development of facile methods for the synthesis of stereochemically defined γ-substituted allylmetal species from readily accessible starting materials has received much attention.[4] Here we report a new method for synthesizing anti homoallylic alcohols in an enantioselective way starting from terminal alkynes and aldehydes (Figure 1). Mechanistically, a transition-metal catalyst and an asymmetric organocatalyst work in relay.[5−7]

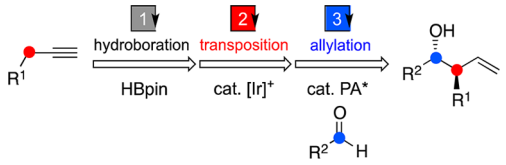
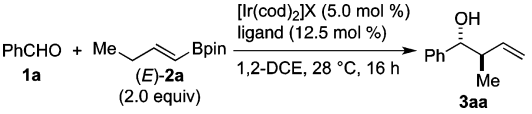


Figure 1. Synthesis of optically active anti homoallylic alcohols starting from terminal alkynes.

We recently reported a convenient method for the diastereoselective synthesis of anti homoallylic alcohols employing 1-alkenylboronates as the precursors of allylboron reagents.[8] A cationic rhodium(I) complex catalyzes the olefin transposition[9] of the 1-alkenylboronate to generate a transient (*E*)-2-alkenylboronate intermediate, which reacts with a coexisting aldehyde in a stereospecific way. However, the rhodium(I)-catalyzed reaction required heating at 90 °C, and the observed anti/syn ratio depended on the double-bond geometry of the 1-alkenylboronate precursor. The *E* isomers, which were more easily prepared and hence were the preferred precursors, showed lower diastereoselectivities (85:15 to 96:4) compared with their *Z* counterparts. We subsequently searched for catalysts of higher activity as well as stereoselectivity and found that cationic iridium(I) catalysts activated by slowly bubbling H_2 directly through the solution for 5 min[10,11] could catalyze the olefin transposition of the *E* isomers even at 28 °C with excellent stereoselectivity. Thus, cationic iridium(I) complexes ([Ir(cod)$_2$]X)[12] were treated with various monodentate phosphine ligands (PR_3) (P/Ir = 2.5) under a hydrogen atmosphere. (*E*)-1-Butenylboronate (*E*)-**2a** was readily prepared by dicyclohexylborane-catalyzed cis hydroboration of but-1-yne with pinacolborane[13] and then reacted with benzaldehyde (**1a**) in the presence of the activated iridium catalyst at 28 °C for 16 h (Table 1). When tetrafluoroborate and PCy_3[14,15] were used as the counterion and the ligand, respectively, anti homoallylic alcohol **3aa** was isolated in 91% yield with almost complete diastereoselectivity (anti/syn = >98:2) (entry 7).

Table 1. Optimization of the Reaction Conditions for the Diastereoselective Allylation of 1a with (*E*)-2a[a]



entry	X	ligand	yield (%)[b]	anti/syn[c]
1	PF_6	PPh_3	3	–
2	PF_6	$P(n\text{-}Bu)_3$	0	–
3	PF_6	PCy_3	78	>98:2
4	PF_6	$P(t\text{-}Bu)_3$	7	–
5	OTf	PCy_3	74	>98:2
6	SbF_6	PCy_3	82	>98:2
7	BF_4	PCy_3	91	>98:2

[a]Conditions: **1a** (0.40 mmol), (*E*)-**2a** (0.80 mmol), [Ir(cod)$_2$]X (5.0 mol %), and ligand (12.5 mol %) in 1,2-dichloroethane (1,2-DCE) (1 mL) at 28 °C for 16 h. [b]Isolated yields. [c]Determined by ^{1}H NMR analysis.

Our previously reported rhodium system[8] required heating at 90 °C for olefin transposition, and the reaction of **1a** with (*E*)-**2a** using [Rh(nbd)(MeCN)$_2$]SbF_6−dppm (90 °C, 12 h) afforded **3aa** in 86% yield with 89:11 dr. When [Rh(nbd)(MeCN)$_2$]-SbF_6−dppm was activated with H_2 in place of [Ir(cod)$_2$]BF_4−PCy_3, the reaction failed to occur at 28 °C. Control experiments were then performed to compare the iridium(I)- and rhodium-

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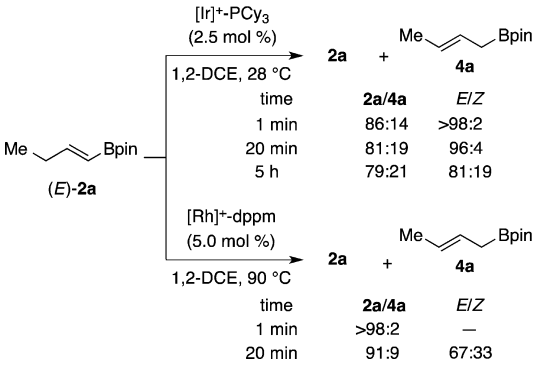
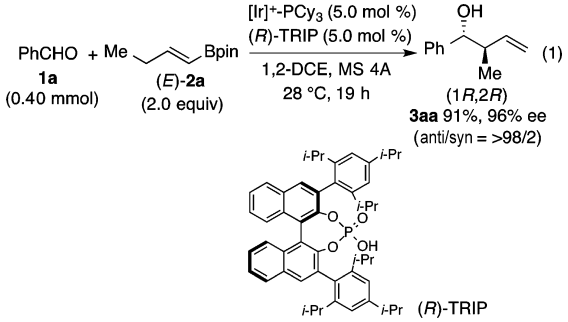
(I)-catalyzed transposition processes in the absence of aldehyde by ^{1}H NMR monitoring (Scheme 1). In the case of iridium, 14% of (*E*)-**2a** isomerized after only 1 min at 28 °C, and the *E* isomer of 2-butenylboronate **4a** was almost completely formed. After 5 h, the *E*/*Z* ratio of **4a** became constant (ca. 4:1). In the case of the rhodium catalyst [Rh(nbd)(MeCN)$_2$]SbF$_6$–dppm, the formation of **4a** was barely observed after 1 min even at 90 °C. After 20 min, 9% of (*E*)-**2a** isomerized to **4a** with an *E*/*Z* ratio of ca. 2:1. Thus, the active iridium catalyst strongly promotes the olefin transposition at 28 °C, and the generation of (*E*)-**4a** is kinetically favored. We assume that as soon as the (*E*)-**4a** is generated, it immediately reacts with a coexisting aldehyde via a six-membered chairlike transition state to produce the anti homoallylic alcohol.

Scheme 1. Control Experiments in the Absence of Aldehyde



The use of cationic iridium(I) complexes rendered it possible to carry out the allylation reaction at temperatures as low as 28 °C, opening a route to asymmetric synthesis. The Antilla group reported that the chiral phosphoric acid (*R*)-TRIP[16] catalyzes a highly enantioselective allylation reaction of **1a** with **4a**.[17] Their work prompted us to examine the iridium(I)-catalyzed reaction of **1a** with **2a** in the presence of (*R*)-TRIP (eq 1). Anti homoallylic alcohol **3aa** was exclusively obtained in 91% isolated yield with a high level of enantioselectivity (96% ee).[18] This result suggested that the activated iridium(I) catalyst and (*R*)-TRIP did not interfere with each other[19] but independently played their roles as catalysts. A large-scale experiment using 670 mg (6.3 mmol) of **1a** also gave a comparable result [1.01 g (91% yield) of **3aa** with 96% ee].

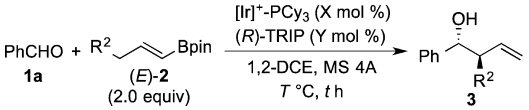


The asymmetric allylation reaction was applied to other terminal alkynes having various simple or functionalized substituents. (*E*)-1-Alkenylboronates **2b–h** were prepared by cis hydroboration of the corresponding terminal alkynes with pinacolborane,[13] and their reactions with **1a** using the activated [Ir]$^+$-PCy$_3$/(*R*)-TRIP catalyst system were examined (Table 2). (*E*)-1-Alkenylboronates **2b–d** having ethyl, isobutyl, and phenyl groups all exhibited high enantioselectivities as well as high yields and excellent diastereoselectivities (entries 1–3). Functional groups such as siloxy, methoxycarbonyl, and chloro groups were allowed at the terminus of the alkyl chain (entries 4–6). On the other hand, only modest diastereo- and enantioselectivities were observed with substrate **2h** having a siloxy group at the C3 position (entry 7).

The scope of aldehydes in the reaction with (*E*)-1-pentenylboronate (*E*)-**2b** was also examined (Table 3). An electronically and sterically diverse array of aromatic aldehydes **1b–f** reacted to give the corresponding anti homoallylic alcohols **3bb–fb** in 85–99% yield with excellent diastereoselectivities and high enantioselectivities (entries 1–5). In addition, *α,β*-unsaturated aldehyde **1g** gave a comparable result (entry 6). Worthy of note was the observation that aliphatic aldehydes such as 3-phenylpropanal (**1h**) and cyclohexanecarbaldehyde (**1i**) also successfully participated in the stereoselective reaction (entries 7 and 8).

Finally, we examined a one-pot, two-step reaction to synthesize anti homoallylic alcohols starting from terminal alkynes (Scheme 2). Terminal alkynes **5a–c** were treated with pinacolborane in the presence of dicyclohexylborane (5.0 mol %) at room temperature or 0 °C for 6–20 h. After the volatile materials were removed under reduced pressure, 1,2-DCE solutions of **1a** and the activated [Ir]$^+$-PCy$_3$/(*R*)-TRIP catalysts were successively added to the residue. The reaction mixture was stirred at 28 or 0 °C, and subsequent chromatographic

Table 2. Asymmetric Allylation Reactions of 1a with Various (*E*)-1-Alkenylboronates 2b–h[a]



entry	2	R^2	X	Y	*T* (°C)	*t* (h)	3	yield (%)[b] (anti/syn)[c]	ee (%)[d]
1	**2b**	Et	5.0	10	28	17	**3ab**	90 (>98:2)	93
2	**2c**	*i*-Bu	5.0	15	0	40	**3ac**	86 (>98:2)	95
3	**2d**	Ph	10	20	−15	64	**3ad**	83 (>98:2)	88
4	**2e**	$(CH_2)_3$OTBS	7.5	20	28	20	**3ae**	85 (>98:2)	90
5	**2f**	$(CH_2)_2CO_2Me$	7.5	10	28	18	**3af**	86 (>98:2)	93
6	**2g**	$(CH_2)_3$Cl	5.0	15	28	18	**3ag**	92 (>98:2)	93
7	**2h**	OTBS	7.5	10	28	44	**3ah**	97 (92:8)	17

[a]Conditions: **1a** (0.40 mmol), (*E*)-**2** (0.80 mmol), [Ir(cod)$_2$]BF$_4$–PCy$_3$ (X mol %, Ir:P = 2:5), (*R*)-TRIP (Y mol %), and MS 4A (50 mg) in 1,2-DCE (1 mL). [b]Isolated yields (averages of 2 runs). [c]Determined by ^{1}H NMR analysis. [d]Determined by chiral HPLC.

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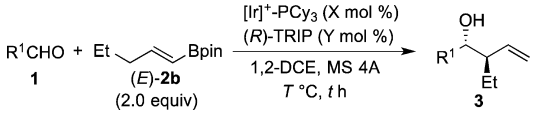
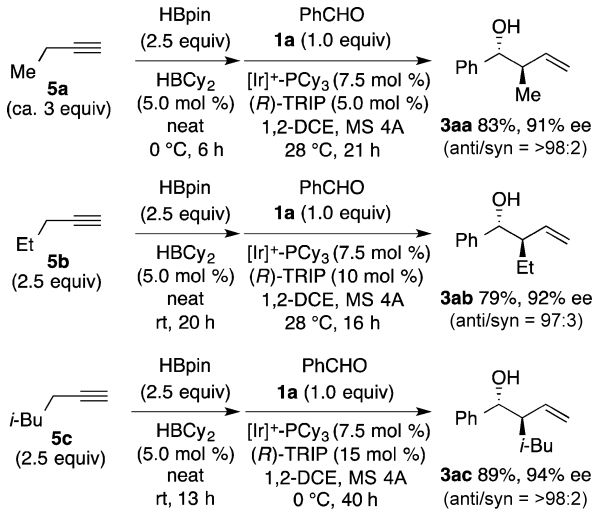
Table 3. Asymmetric Allylation Reactions of Various Aldehydes 1b–i with (*E*)-2b[a]



entry	1	R^1	X	Y	T (°C)	t (h)	3	yield (%)[b] (anti/syn)[c]	ee (%)[d]
1	**1b**	4-$NO_2C_6H_4$	5.0	10	28	20	**3bb**	85 (>98:2)	95
2	**1c**	4-$MeOC_6H_4$	7.5	15	28	17	**3cb**	99 (>98:2)	92
3	**1d**	4-MeC_6H_4	7.5	10	28	20	**3db**	87 (>98:2)	90
4	**1e**	2-MeC_6H_4	10	20	0	72	**3eb**	98 (>98:2)	92
5	**1f**	2-furyl	5.0	10	28	38	**3fb**	91 (>98:2)	92
6	**1g**	PhCH=CH	5.0	10	28	19	**3gb**	96 (>98:2)	93
7	**1h**	$PhCH_2CH_2$	10	20	5	64	**3hb**	88 (>98:2)	91
8	**1i**	Cy	10	20	5	64	**3ib**	82 (97:3)	88

[a]Conditions: **1** (0.40 mmol), (*E*)-**2b** (0.80 mmol), [Ir(cod)$_2$]BF_4–PCy_3 (X mol %, Ir:P = 2:5), (*R*)-TRIP (Y mol %), and MS 4A (50 mg) in 1,2-DCE (1 mL). [b]Isolated yields (averages of 2 runs). [c]Determined by ^{1}H NMR analysis. [d]Determined by chiral HPLC.

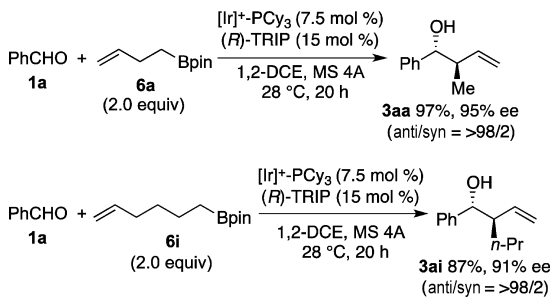
Scheme 2. One-Pot Cis Hydroboration/Olefin Transposition/Allylation Reaction



purification afforded the corresponding anti homoallylic alcohols **3aa**–**3ac** in good overall yields with high enantioselectivities. Accessibility of starting materials is one of the most important criteria for synthetically useful organic reactions. All of the starting materials required for the present reaction are readily available, even from commercial sources.

To further expand the synthetic utility of this relay system, we employed 3- and 5-alkenylboronates **6a** and **6i** as the allylboron precursors (Scheme 3). The reaction proceeded smoothly to give anti homoallylic alcohols **3aa** and **3ai** in high yields, and the stereoselectivities observed were similar to those of (*E*)-1-alkenylboronates **2**. It is noteworthy that olefin transposition takes place multiple times from a position remote to the boryl group.[20]

Scheme 3. Asymmetric Allylation Reactions of 1a with 3- and 5-Alkenylboronates 6a and 6i



In summary, we have demonstrated that a cationic iridium(I) complex/chiral phosphoric acid relay system provides a highly diastereo- and enantioselective route to anti homoallylic alcohols starting from terminal alkynes and aldehydes. A cationic iridium(I) complex promotes the olefin transposition of 3- and 5-alkenylboronates as well as (*E*)-1-alkenylboronates at 28 °C, thus generating in situ (*E*)-2-alkenylboronates that are often laborious to prepare stereoselectively. The asymmetric allylation reaction catalyzed by a chiral phosphoric acid is compatible with the cationic iridium(I) complex.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) The H_2 activation was important to enhance the activity of $[Ir(cod)_2]BF_4$–PCy_3. Without H_2 activation, the reaction was much slower even at 90 °C.

(12) Other transition-metal complexes such as $RhH(PPh_3)_4$, $CpPd(\pi\text{-allyl})$–$P(t\text{-Bu})_3$, $RuCl_2(PPh_3)_3$, and $RuH_2(CO)(PPh_3)_3$ were not effective.

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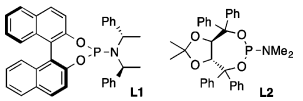
(15) Other monodentate phosphines, including chiral ones [PPh_2Me, $PPhMe_2$, PMe_3, $P(n\text{-Pr})_3$, $P(n\text{-Bu})(1\text{-Ad})_2$, (*S*)-MOP, **L1**, **L2**], failed to afford **3aa**, and the starting materials were recovered. Bidentate phosphine ligands [dppm, dppe, dppf, dcype] were not effective either.



(16) (a) Akiyama, T. WO 2004096753, 2004; *Chem. Abstr.* **2004**, *141*, 411087. (b) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424. For seminal work on chiral phosphoric acids, see: (c) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. (d) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.

(17) (a) Jain, P.; Antilla, J. C. *J. Am. Chem. Soc.* **2010**, *132*, 11884. For a mechanistic study, see: (b) Grayson, M. N.; Pellegrinet, S. C.; Goodman, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 2716.

(18) The enantioselectivity was slightly better in the presence of 4 Å molecular sieves (MS 4A). For a similar effect of MS 4A, see: Jain, P.; Wang, H.; Houk, K. N.; Antilla, J. C. *Angew. Chem., Int. Ed.* **2012**, *51*, 1391.

(19) The reaction of $[Ir(cod)_2]BF_4$ with (*R*)-TRIP was monitored by ^1H and ^{31}P NMR spectroscopy. Upon activation with H_2, the 1,5-cyclooctadiene (cod) ligand of $[Ir(cod)_2]BF_4$ was completely hydrogenated to form cyclooctane together with unidentified iridium complexes. Then, (*R*)-TRIP was added to the resulting reaction mixture, and no significant change was observed. On the basis of these results and the much stronger acidity of HBF_4 than (*R*)-TRIP, we assume that $[Ir(PCy_3)_2(L)_n]BF_4$ is more likely to be the active species than $[Ir(PCy_3)_2(L)_n][(R)\text{-TRIP}]$. For the p$K_a$ values of (*R*)-TRIP, see: Christ, P.; Lindsay, A. G.; Vormittag, S. S.; Neudörfl, J.-M.; Berkessel, A.; O'Donoghue, A. C. *Chem.—Eur. J.* **2011**, *17*, 8524.

(20) For recent examples of chain-walking processes, see: (a) Kochi, T.; Hamasaki, T.; Aoyama, Y.; Kawasaki, J.; Kakiuchi, F. *J. Am. Chem. Soc.* **2012**, *134*, 16544. (b) Mei, T.-S.; Werner, E. W.; Burckle, A. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 6830 and references therein. Also see: (c) Shen, X.; Wasmuth, A. S.; Zhao, J.; Zhu, C.; Nelson, S. G. *J. Am. Chem. Soc.* **2006**, *128*, 7438.

■ NOTE ADDED AFTER ASAP PUBLICATION

Due to a production error, this paper was published on the Web with errors in Scheme 2. The corrected version was reposted on July 30, 2013.