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Title: Rh-Catalyzed Reaction of Propargylic Alcohols with Aryl Boronic Acids–Switch from β-OH Elimination to Protodemetalation

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Asymmetric Intramolecular Hydroalkoxylation of Unactivated Alkenes Catalyzed by Chiral *N*-Triflyl Phosphoramide and $TiCl_4$

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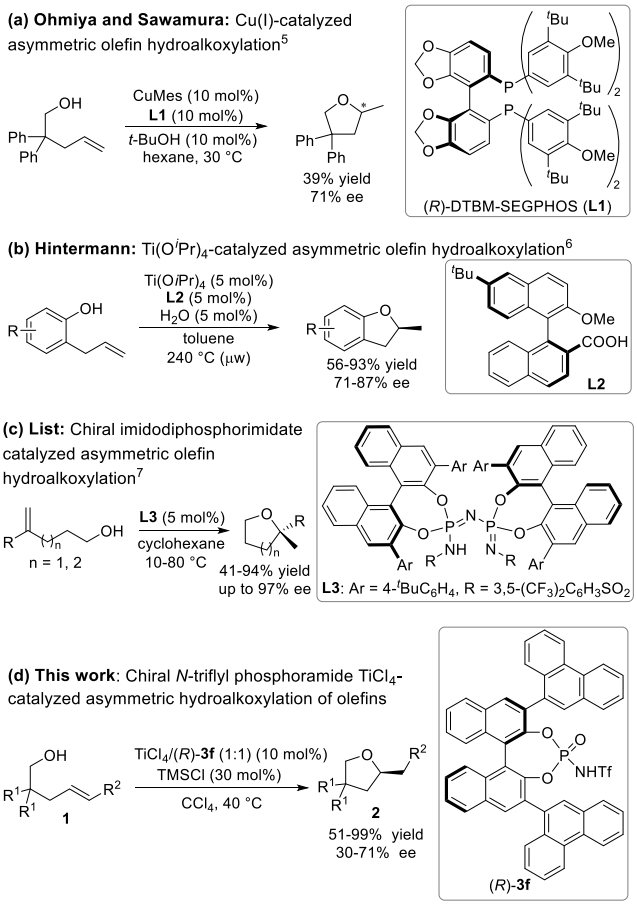
Summary of main observation and conclusion By using a combination of a chiral *N*-triflyl phosphoramide and $TiCl_4$ as the catalyst, a new process for asymmetric intramolecular hydroalkoxylation of unactivated alkenes was developed, producing various chiral tetrahydrofuran derivatives in 51-99% yields with 30-71% ee's.

Background and Originality Content

Hydroalkoxylation of alkenes is defined as addition of an alcohol group to a C-C double bond, which provides an atom-economical and highly straightforward way for the synthesis of ethers with increased value from readily available olefins.[1] Although non-asymmetric hydroalkoxylation of unactivated olefins has been achieved by using strong Lewis acids,[2] Brønsted acids,[3] or transition metals[4] as the catalyst, development of asymmetric processes still remains a formidable challenge in organic chemistry. Recently, asymmetric hydroalkoxylation of unactivated alkenes has been sporadically reported.[5-9] For example, in 2015 Sawamura and co-workers used (*R*)-DTBM-SEGPHOS-Cu(I) complex as the catalyst for asymmetric intramolecular hydroalkoxylation of an alkenol to give the corresponding chiral tetrahydrofuran in a 39% yield with 71% ee (Scheme 1a).[5] At the same time, Hintermann and co-workers developed asymmetric intramolecular hydroalkoxylation of allylphenols to chiral 2-methylcoumarans in the presence of 5 mol% of $Ti(OiPr)_4$-**L2** under microwave irradiation, affording chiral 2-methylcoumarans in 56-93% yields with 71-87% ee's (Scheme 1b).[6] Very recently, List and co-workers developed chiral Brønsted acid catalyzed asymmetric intramolecular hydroalkoxylation of 1,1-disubstituted alkenes by using chiral imidodiphosphorimidate **L3** as the catalyst to produce various chiral tetrahydrofurans and tetrahydropyrans with yields of up to 94% and ee's of up to 97% (Scheme 1c).[7] In addition, chiral salen-Co catalyzed and enzymatic asymmetric intramolecular hydroalkoxylations also were respectively developed by Shigehisa and coworkers,[8] and Yang and coworkers.[9] Chiral phosphoric acids and *N*-triflyl phosphoramides have been widely used as acid-base cooperative organocatalysts for various asymmetric catalysis.[10] However, their Brønsted acidity is generally not strong enough to promote hydroalkoxylation of unactivated olefins. By combining a chiral *N*-triflyl phosphoramide and strong Lewis acid $TiCl_4$, we achieved catalytic asymmetric hydroalkoxylation of alkenols to produce chiral tetrahydrofurans[11] under mild conditions (Scheme 1d). Herein, we report our results on the project.

Scheme 1 Catalytic asymmetric intramolecular hydroalkoxylation of unactivated alkenes.



Results and Discussion

Studies started with the investigation of the hydroalkoxylation of alkenol **1a** [Table 1 and Table S1 in Supporting Information (SI)]. The reaction went smoothly to form substituted tetrahydrofuran **2a** in 99% yield in the presence of 50 mol% of $TiCl_4$, whereas HCl[3b] did not promote the hydroalkoxylation under otherwise the same conditions (Table 1, entry 2 vs 3). This demonstrated that the active catalyst for the reaction likely was the strong Lewis acid $TiCl_4$, not its "hidden Brønsted acid" HCl.[12] A decrease in the amount of $TiCl_4$ to 10 mol% almost completely eliminated the transformation probably due to hydrolysis of $TiCl_4$ by the moisture

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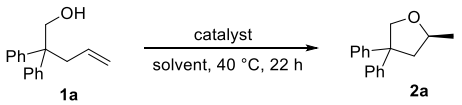
in the reaction

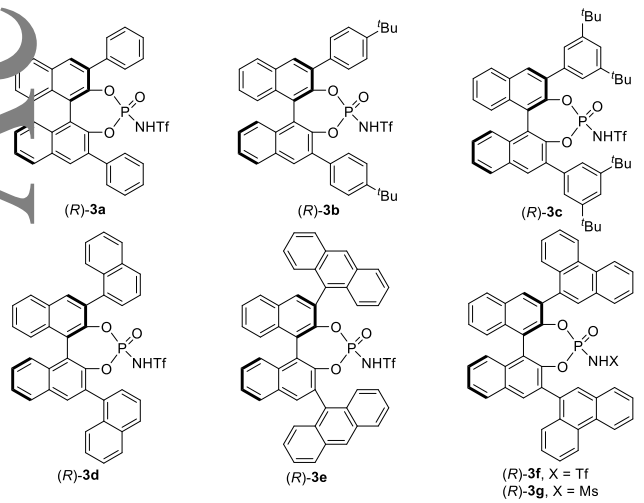
Table 1 Investigation of reaction conditions[a]



entry	catalyst	additive	sol.	yield[b]	ee[c]
1	$TiCl_4$	-	DCM	trace	-
2[d]	$TiCl_4$	-	DCM	99%	-
3[e]	HCl	-	DCM	0%	-
4	$TiCl_4$/BINOL	-	DCM	0%	-
5	$TiCl_4$/**3a**	-	DCM	95%	15%
6	**3a**	-	DCM	0%	-
7	$TiCl_4$/**3d**	-	DCM	96%	10%
8	$TiCl_4$/**3e**	-	DCM	97%	44%
9	$TiCl_4$/**3e**	TMSCl	DCM	98%	48%
10	$TiCl_4$/**3b**	TMSCl	DCM	95%	14%
11	$TiCl_4$/**3c**	TMSCl	DCM	94%	14%
12	$TiCl_4$/**3f**	TMSCl	DCM	92%	59%
13[f]	$TiCl_4$/**3g**	TMSCl	CCl_4	50%	58%
14	$TiCl_4$/**3f**	TMSCl	CCl_4	90%	71%
15	$Ti(O^iPr)_4$/**3f**	TMSCl	CCl_4	0%	-
16	$AlCl_3$/**3f**	TMSCl	CCl_4	23%	0%
17	$SnCl_4$/**3f**	TMSCl	CCl_4	84%	0%
18	$FeCl_3$/**3f**	TMSCl	CCl_4	97%	0%

[a]All reactions were performed with **1a** (0.91 mmol), MXn (0.091 mmol, 10 mol%), (*R*)-**3** (0.091 mmol, 10 mol%), TMSCl (0.0273 mmol, 30 mol%) in solvent (1.5 mL) at 40 °C for 22 h unless otherwise stated. The absolute configuration of **2a** was determined as *S* by X-ray crystallography. [b]Isolated yields based on **1a**. [c]Enantiomeric excesses were determined by chiral HPLC analysis. [d]50 mol% of $TiCl_4$ was used. [e]82 mol% of dry HCl was used. [f]The reaction was performed with **1a** (0.25 mmol), $TiCl_4$ (0.025 mmol, 10 mol%), (*R*)-**3g** (0.025 mmol, 10 mol%), TMSCl (0.075 mmol, 30 mol%) in CCl_4 (0.45 mL) at 40 °C for 22 h.

Scheme 2 Phosphoramides 3 examined.



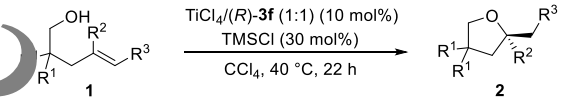
system (Table 1, entry 1). However, the reaction became active again when introducing additional 10 mol% of chiral *N*-triflyl phosphoramide (*R*)-**3a** (Table 1, entry 5). But the phosphoramide (*R*)-**3a** itself couldn't promote the hydroalkoxylation (Table 1, entry 6), implying that (*R*)-**3a** likely served as a ligand to stabilize $TiCl_4$ and also contribute the enantiocontrol during the catalysis. The additive trimethylsilyl chloride (TMSCl) could eliminate the moisture and thus protected the $TiCl_4$ species from hydrolysis, making the reaction much more reproducible without any loss of yield and enantioselectivity (Table 1, entry 9 vs 8). Further studies showed that phosphoramide (*R*)-**3f** exhibited the highest enantioselectivity for the reaction, to give the corresponding chiral tetrahydrofuran **2a** in a 92% yield with 59% ee (Table 1, entry 12 vs entries 5, 7-11, and 13, and Scheme 2). The absolute configuration of **2a** was determined as *S* by X-ray analysis (see SI). The ee value can be further improved to 71% when tetrachloromethane (CCl_4) was chosen as the solvent for the reaction (Table 1, entry 14). Lowering reaction temperature from 40 ℃ to 25 ℃ resulted in a similar ee but a much lower isolated yield (SI, Table S1, entry 15 vs 14). An increase in the amount of phosphoramide (*R*)-**3f** led to an obvious decrease of enantioselectivity (SI, Table S1, entry 14 vs 18-19). The replacement of $TiCl_4$ with other strong Lewis acids ($AlCl_3$, $SnCl_4$, or $FeCl_3$) or of phosphoramide (*R*)-**3f** with BINOL resulted in disappearance of enantioselectivity or conversion (Table 1, entries 15-18 and 4). Control experiments showed that the $AlCl_3$, $SnCl_4$, and $FeCl_3$ catalytic systems could not promote racemization of enantioenriched tetrahydrofuran **2a** (see SI), implying these corresponding catalytic systems did not have stereoselective induction for the hydroalkoxylation.

Under the optimized reaction conditions, the substrate scope was then examined for the asymmetric hydroalkoxylation with 10 mol% $TiCl_4$ and 10 mol% chiral *N*-triflyl phosphoramide (*R*)-**3f** as the catalyst (Table 2). Various 2,2-disubstituted terminal alkenols **1a-h** underwent asymmetric intramolecular hydroalkoxylation to give the corresponding chiral tetrahydrofuran derivatives **2a-h** in 63-99% yields with 42-71 ee's (Table 2, entries 1-8). The electronic property of the 2,2-substituents seems to have little impact on the reaction in terms of reactivity and enantioselectivity (Table 2, entries 1-4 vs entry 5). Alkenol substrates bearing an internal double bond such as compounds **1i** and **1j** displayed obviously lower reactivity for the transformation (Table 2, entries 9 and 10). The corresponding hydroalkoxylations were carried out at an increased temperature (60 ℃ vs 40 ℃), forming chiral tetrahydrofurans **2i** and **2j** in lower yields and with decreased ee's. No six-membered products were observed for the two substrates although the corresponding 6-endo-trig cyclization was also allowed by Baldwin's rules. Alkenol **1k** having a phenyl substituent at the internal carbon of the double bond underwent intramolecular hydroalkoxylation to produce **2k** in 85% yield but without any enantioselectivity (Table 2, entry 11). The substrate was even active for the hydroalkoxylation with *N*-triflyl phosphoramide (*R*)-**3f** as the catalyst without $TiCl_4$, but resulting in similar reaction results (90% yield, 0% ee). Alkenols with one carbon longer chain between the hydroxyl group and the C-C double bond such as 2,2-diphenylhex-5-en-1-ol were ineffective for the reaction.

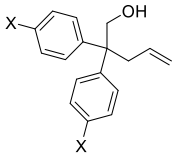
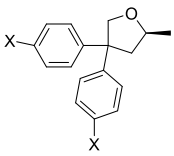
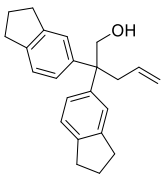
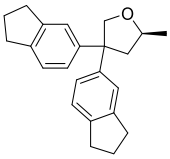
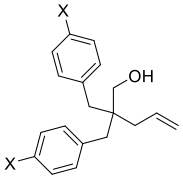
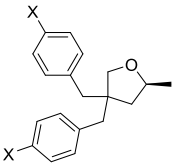
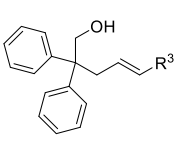
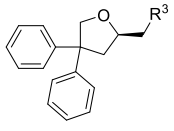
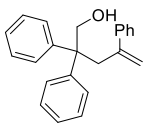
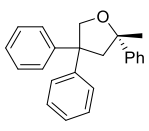
The two phenyl substituents of **1a** was crucial for its intramolecular hydroalkoxylation activity. Replacement of the phenyl substituents with methyl groups (**1l**) or hydrogens (**1m**) led to a dramatic decrease in the yield of cyclization product **2l** or even a complete deactivation for the formation of **2m** (Scheme 3a). These results demonstrated that the phenyl substituents had an obvious Thorpe-Ingold effect on the intramolecular hydroalkoxylation.[13] Reaction of 2-allylphenol (**1n**) under the standard conditions did not give the corresponding cyclized

hydroalkoxylation product, but produced hydrochlorination product **4** (Scheme 3b). No isomerization of the C-C double bond of **1n** was observed during the reaction and $TiCl_4$ catalyst was necessary for the chlorination, implying the transformation likely proceeded via a Lewis acid catalyzed process.

Table 2 Investigation of the substrate scope for the catalytic asymmetric hydroalkoxylation of olefins[a]

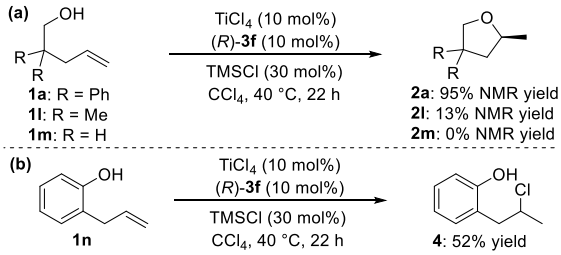


1 2

entry	1	2	yield[b] (ee)[c]
			
1	X = H, **1a**	X = H, **2a**	90% (71%)
2	X = Me, **1b**	X = Me, **2b**	99% (69%)
3	X = ^{n}Pr, **1c**	X = ^{n}Pr, **2c**	86% (67%)
4	X = Ph, **1d**	X = Ph, **2d**	90% (42%)
5	X = Cl, **1e**	X = Cl, **2e**	93% (71%)
			
6	**1f**	**2f**	97% (62%)
			
7	X = H, **1g**	X = H, **2g**	75% (61%)
8	X = Me, **1h**	X = Me, **2h**	63% (67%)
			
9[d,e]	R^3 = Me, **1i**	R^3 = Me, **2i**	73% (30%)
10[d,e]	R^3 = ^{n}Pr, **1j**	R^3 = ^{n}Pr, **2j**	51% (33%)
			
11[e]	**1k**	**2k**	85% (0%)[f] 90% (0%)[g]

[a]All reactions were performed with **1** (0.91 mmol), $TiCl_4$ (0.091 mmol, 10 mol%), (*R*)-**3f** (0.091 mmol, 10 mol%), TMSCl (0.273 mmol, 30 mol%) in CCl_4 (1.5 mL) at 40 °C for 22 h unless otherwise stated. The absolute configuration of **2a** was determined as *S* by X-ray crystallography and those of **2b-j** were tentatively assigned as *S* by analogy. [b]Isolated yields based on **1**. [c]Enantiomeric excesses were determined by chiral HPLC analysis. [d]The reaction was carried out with **1** (0.455 mmol), $TiCl_4$ (0.091 mmol), (*R*)-**3f** (0.091 mmol), TMSCl (0.273 mmol) in CCl_4 (1.0 mL) at 60 ℃ for 22 h. [e]No 6-membered cyclized products were observed as judged by ^{1}H NMR analysis of the crude reaction mixtures, so regioselectivities were greater than 20:1. [f]Reaction time was 12 h. [g]The reaction was carried out with **1** (0.91 mmol, 10 mol%), (*R*)-**3f** (0.091 mmol, 10 mol%) in CCl_4 (1.5 mL) at 40 °C for 22 h.

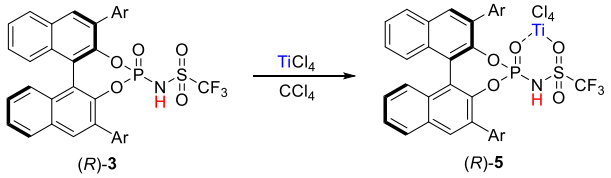
Scheme 3 Control experiments.



In the absence of $TiCl_4$, the *N*-triflyl phosphoramides (*R*)-**3** alone could not promote the hydroalkoxylation of **1a** (Table 1, entry 6). This implied that the active catalytic species likely be a complex formed between (*R*)-**3** and $TiCl_4$ (Scheme 4).[14] The Ti(IV)-(*R*)-**3** complex may serve either as a chiral Lewis acid or as a chiral super strong Brønsted acid to catalyze the asymmetric hydroalkoxylation. We preferred the Lewis acid-catalyzed process based on the following considerations. (1) The combination of $TiCl_4$ and *N*-mesyl phosphoramide (*R*)-**3g** also displayed catalytic activity for the reaction (Table 1, entry 13), despite the much lower Brønsted acidity as compared to *N*-triflyl phosphoramide (*R*)-**3f**. (2) A possible carbon cation intermediate generated during a Brønsted acid catalyzed process may trigger the isomerization of the double bond to a more stable one, but no isomerization occurred in the treatment of **1n** with (*R*)-**3f** and $TiCl_4$ as judged by ^{1}H NMR analysis of the crude reaction mixture (Scheme 3b).

On the other hand, the formation of the Ti(IV)-(*R*)-**3** complex can greatly increase in the Brønsted acity of *N*-triflyl phosphoramide (*R*)-**3**.[14-16] So it is also possible that the complex acted as a chiral super strong Brønsted acid catalyst for the hydroalkoxylation.[14-16] At this point we have not been able to completely eliminate this mechanistic possibility.

Scheme 4 The Proposed complex formed between 3 and $TiCl_4$.



Conclusions

In summary, we have developed a new process for asymmetric intramolecular hydroalkoxylation of unactivated olefins by using a combination of *N*-triflyl phosphoramide (*R*)-**3** and $TiCl_4$ as catalyst. Although the enantioselectivity is moderate, this work has provided a new catalytic strategy for asymmetric hydroalkoxylation of challenging unactivated olefins.

Supporting Information

The Supporting Information is available free of charge on the WWW under https://doi.org/10.1002/cjoc.2019xxxxx. Synthetic procedure, characterization data, spectroscopic spectra, and chromatograms for ee determination (pdf), Crystallographic data for **2a** (CIF).

Accession Codes

CCDC 1863034 contains the supplementary crystallographic data for compound **2a**. These data can be obtained free of charge v www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_ -quest@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallo-graphic Data Centre, 12 Union Road, Cambridge CB2 1EZ, ; fax: +44 1223 336033.

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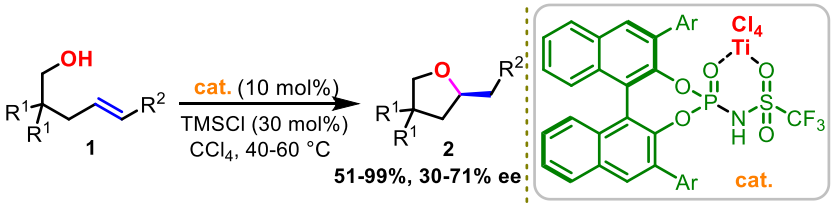
Asymmetric Intramolecular Hydroalkoxylation of Unactivated Alkenes Catalyzed by Chiral *N*-Triflyl Phosphoramide and $TiCl_4$

Pengyuan Zhao, Aolin Cheng, Xinxu Wang, Jiguo M[illegible], Guoqing Zhao,* Yingkun Li, Yi Zhang, Baoguo Zhao*



A combination of *N*-triflyl phosphoramide and $TiCl_4$ challenges asymmetric hydroalkoxylation of unactivated alkenes.

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