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A Room-Temperature Catalytic Asymmetric Synthesis of Allenes with ECNU-Phos

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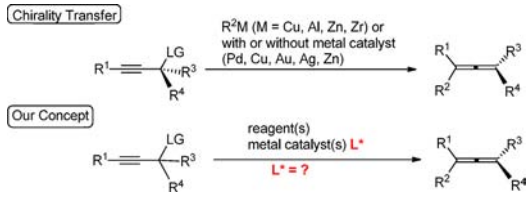
Supporting Information

ABSTRACT: Three-carbon axial chirality has been asymmetrically established from racemic one-carbon central chirality efficiently at room temperature: we report here the discovery of the first catalytic asymmetric carbonylation of readily available racemic propargylic carbonates to access optically active 2,3-allenoates with fairly high ee. The combination of $[(\pi\text{-allyl})PdCl]_2$ with [(*R*)-**ECNU-Phos**], a new chiral bisphosphine ligand based on a biphenyl skeleton, demonstrates high enantioselectivity. Both enantiomers of allenoates can be obtained at room temperature by applying either (*R*)- or (*S*)-**ECNU-Phos**.

Asymmetric synthesis has always been a very popular and hot topic in the science of synthesis because there are so many naturally occurring optically active compounds with biological importance.[1] Historically, so much attention has been focused on establishing one-carbon central chirality with many well-established protocols, showing even industrial applications.[2] Axial chirality is also a very important part of asymmetric synthesis: the construction of axial chirality in biaryl compounds, such as chiral BINAP, can be easily established through optical resolution from the racemic mixture[3] or direct introduction of phosphinyl groups into an optically active binaphthyl framework via Ni-assisted coupling;[4] however, the establishment of axial chirality of allenes, which spreads over three carbon atoms, is still a conundrum.[5,6]

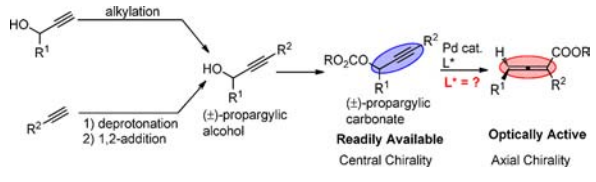
In the meantime, allenes have become more and more important because many naturally occurring products with biopotential contain an allene unit[7] and allenes also serve as very important building blocks for organic synthesis;[8−10] (*S*)-2,4-bis(2-(3,5-bis(trifluoromethyl)phenyl)phosphino)phenyl-5,5-dimethylhexa-2,3-diene has even been demonstrated as a chiral ligand in Rh-catalyzed enantioselective addition of arylboronic acids to α-keto esters.[11] Therefore, efficient approaches to chiral allenes are highly desirable. The most common and efficient approaches involve chirality transfer from optically active propargylic derivatives with a proper leaving group.[12] However, in all of these known cases, at least a stoichiometric amount of optically active starting compound is required and racemization is in most cases a serious problem. We envisioned a catalytic system that could lead to highly optically active allenes from readily available racemic propargylic derivatives (Scheme 1).[13] The challenge would be the interconversion between the pair of involved diastereomeric propargyl/allenyl metallic intermediates favoring one for a high enantioselectivity (cf. Scheme 4).

Scheme 1. Central-to-Axial Chirality: Optically Active Approach versus Racemic Approach



As a first try for this strategy (Schemes 1 and 2), we explored the carbonylation of readily available racemic propargylic derivatives to afford 2,3-allenoates efficiently,[14] provided that a suitable chiral ligand for such a transformation could be identified (Scheme 2). After tedious work, such axial chirality was efficiently established from central chirality: we here report the discovery of the first catalytic asymmetric carbonylation of readily available racemic propargylic carbonates bearing central chirality to access optically active 2,3-allenoates.[15] The key finding is a newly identified chiral bisphosphine ligand based on a biphenyl skeleton, (*R*)- or (*S*)-**ECNU-Phos**, which works at energy-effective room temperature to prevent possible racemization,[16] together with $[(\pi\text{-allyl})PdCl]_2$ for high enantioselectivity and efficiency. Both enantiomers of the allenoate can be obtained at room temperature and 1 atm of CO by applying either (*R*)- or (*S*)-**ECNU-Phos**.

Scheme 2. Design of a Catalytic Approach To Synthesize Chiral 2,3-Allenoates



On the basis of our previous results with optically active propargylic mesylates using $Pd(dba)_2$ and (*S*)-Segphos as the catalyst with 1.1 equiv of $(NH_4)_2HPO_4$ as the base,[14] our initial

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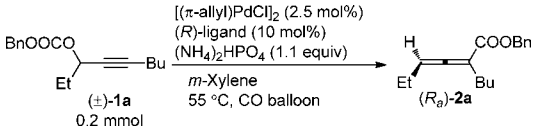
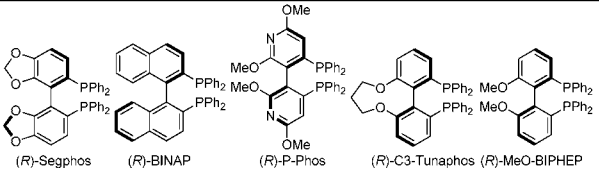
experiments began with the carbonylation of racemic benzyl non-4-yn-3-yl carbonate (**1a**) under the catalysis of $Pd(dba)_2$ and (*R*)-Segphos. To our delight, when $[(\pi\text{-allyl})PdCl]_2$ was used, this reaction occurred at 55 °C to afford (R_a)-**2a** in 70% yield with 48% ee (Table 1, entry 1) (for screening of different Pd catalysts, see Table S1 in the Supporting Information). On the basis of this result, we identified bisphosphine ligands as the best skeletons among so many well-established chiral ligands (for some typical results with other ligands, see Table S2).[3] Next, some commercially available chiral diphosphine ligands were examined.[17] (*R*)-BINAP gave a better result (66% yield with 65% ee), but the ligand based on the bipyridyl skeleton, (*R*)-P-Phos, only led to 21% ee (entries 2 and 3). When (*R*)-C3-Tunaphos was used, (R_a)-**2a** could be prepared in only 44% yield with 63% ee (entry 4). Interestingly, higher enantioselectivity was observed with the rather simple ligand (*R*)-MeO-BIPHEP (entry 5).

Table 1. Effect of Ligand Skeletons with the Basic Setting of PPh_2



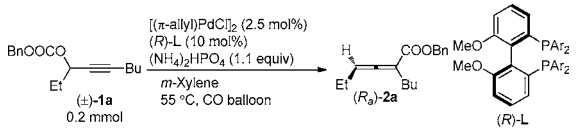
Entry	Ligand	Time (h)	Yield (%) of (R_a)-**2a** [a]	**1a** (%)[b]
1	(*R*)-Segphos	9	70 (48)	3
2	(*R*)-BINAP	5	66 (65)	16
3	(*R*)-P-Phos	5	49 (21)	28
4	(*R*)-C3-TunaPhos	5	44 (63)	43
5	(*R*)-MeO-BIPHEP	4	61 (71)	18



[a]Isolated yields; the % ee's of **2a** are shown in parentheses. [b]Determined by ^1H NMR analysis using 1,3,5-trimethylbenzene as the internal standard.

With the results for (*R*)-MeO-BIPHEP in hand, we worked to identify the best aryl substituent of the coordinating phosphorus center with the goal of tuning its electronic and steric nature for practical enantioselectivity.[18] No reaction occurred with the 2-furyl ligand [(*R*)-**L1**] (Table 2, entry 1). When the 4-position of the phenyl group was substituted with methyl [(*R*)-**L2**], the yield was improved but the ee dropped slightly (entry 2). The 3,5-dimethylphenyl-substituted ligand [(*R*)-**L3**] made both the yield and ee drop sharply (entry 3). All these facts indicated that tuning of the electronic nature may not work very well, which made us turn our attention to the steric effect. Increasing the steric hindrance at the 3,5-positions by replacing Me with *t*-Bu [(*S*)-**L4**] led to a higher ee (entry 4). When OMe was introduced at the 4-position of the aryl group of (*S*)-**L4** [(*R*)-**L5**], the enantioselectivity was further improved, albeit slightly (entry 5). Interestingly, removing the 3,5-di-*tert*-butyl groups from (*R*)-**L5** [(*R*)-**L6**] provided very comparable results: 48% yield of (R_a)-**2a** with 63% ee (entry 6). At the point of nowhere, it was observed that when the methoxy group was relocated from the 4-position to the 3-position of the phenyl ring [(*R*)-**L7**], the rate of the reaction increased together with a remarkable increase in enantioselectivity: 57% yield of the 2,3-allenoate with 79% ee (entry 7). Excitingly, the additional introduction of a 5-OMe group [(*R*)-**L8**, denoted as **ECNU-Phos**] gave a much better result: the 2,3-allenoate was obtained in 51% yield with 84% ee within 2 h at 55 °C and in 69% yield with 83% ee after 7 h of stirring at 45 °C (entries 8 and 9).[19] It was amazing to notice the difference between methyl and methoxy groups (entry 9 vs 3).

Table 2. Tuning of the Aryl Group in BIPHEP-Type Ligands



Entry	Ar ((*R*)-**L**)	*t* (h)	Yield of **2a** (%)[a]	**1a** (%)[b]
1	2-furyl (**L1**)[c]	5	0	97
2	4-MeC_6H_4 (**L2**)[c]	5	75 (69)	2
3	3,5-$Me_2C_6H_3$ (**L3**)[c]	5	58 (56)	5
4	3,5-(*t*-Bu)$_2C_6H_3$ (**L4**)[c,d]	5	47 (−60)	33
5	3,5-(*t*-Bu)$_2$-4-$MeOC_6H_2$ (**L5**)[c]	5	14 (66)	60
6	4-$MeOC_6H_4$ (**L6**)[e]	9	48 (63)	3
7	3-$MeOC_6H_4$ (**L7**)[e]	2	57 (79)	14
8	3,5-$(MeO)_2C_6H_3$ (**L8**)[f]	2	51 (84)	23
9	3,5-$(MeO)_2C_6H_3$ (**L8**)[g]	7	69 (83)	4

[a]Isolated yields; the ee's of **2a** are shown in parentheses. [b]Determined by ^1H NMR analysis using 1,3,5-trimethylbenzene as the internal standard. [c]The chiral ligands were bought from Strem Chemicals. [d](*S*)-**L4** was used since only the *S* isomer is commercially available. [e]Prepared according to ref 19. [f]Newly prepared for the first time according to ref 19. [g]This reaction was carried out at 45 °C.

Moreover, base and solvent effects were also examined. LiF and toluene were identified as the best (Tables S3 and S4). The scope of such an efficient strategy was then explored by conducting the reactions of racemic propargylic carbonates, $[(\pi\text{-allyl})PdCl]_2$ (1−2 mol %), (*R*)-**ECNU-Phos** (4−8 mol %), and LiF (1.1 equiv) with a CO balloon in toluene at 25 °C, and the results are shown in Table 3. For substrates with $R^1 = R^2$ = alkyl, 2 mol % $[(\pi\text{-allyl})PdCl]_2$ and 8 mol % (*R*)-**ECNU-Phos** were needed to obtain 2,3-allenoates (R_a)-**2a**−**e** in 58−64% yield with 88−92% ee after 24 h. Interestingly, with R^1 = aryl, the reaction of methyl 1-phenyl-2-heptynyl carbonate (**1f**) also proceeded, affording the corresponding product (R_a)-**2f** at room temperature with an even higher enantioselectivity (93% ee) using only 1 mol % $[(\pi\text{-allyl})PdCl]_2$ and 4 mol % (*R*)-**ECNU-Phos**. As expected, (S_a)-**2f** could also be synthesized with similar results (78% yield and 94% ee) by applying the other enantiomer, (*S*)-**ECNU-Phos** (eq 1); in fact, this result was quite general with R^1 being a differently alkyl-substituted aryl group: R^2 could be alkyl [(R_a)-**2g**−**i**], phenethyl [(R_a)-**2j**], or cycloalkyl [(R_a)-**2k** and (R_a)-**2l**]. Furthermore, when either an electron-donating group (OMe) or an electron-withdrawing group (e.g., Cl, Br) was introduced on the phenyl ring of R^1, 1.5 mol % $[(\pi\text{-allyl})PdCl]_2$ and 6 mol % (*R*)-**ECNU-Phos** were required, affording very decent enatioselectivities. Finally, it is interesting to note that an allyl group (**1r**) could also be accommodated. These versatile substituents such as OMe, Cl, Br, and allyl will surely provide opportunities for further synthetic elaboration. It should be noted that in some cases some of the starting carbonate was

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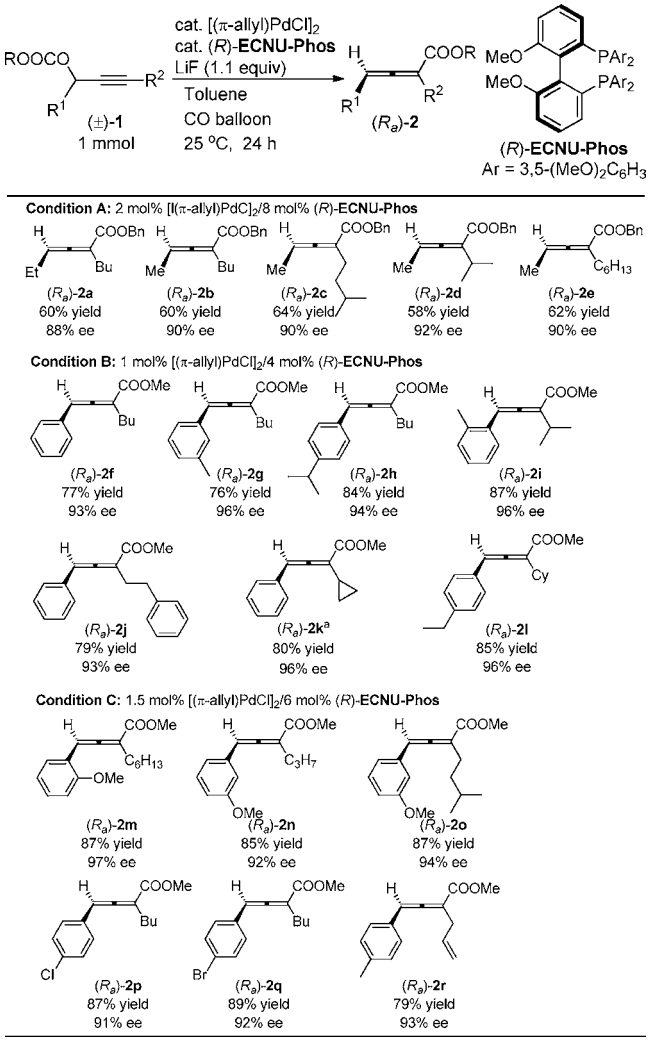
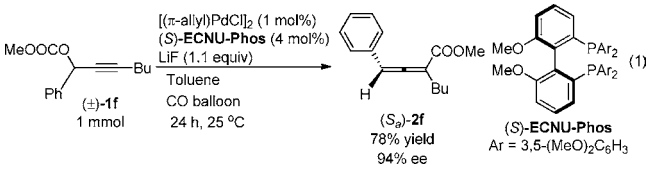
Table 3. Substrate Scope of Pd-Catalyzed Asymmetric Carbonylation of Racemic Propargylic Carbonates



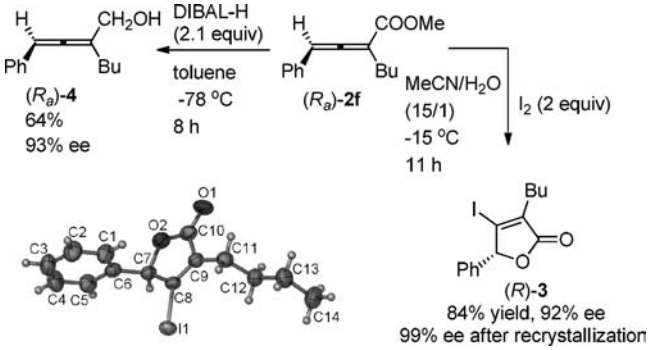
[a]The reaction was carried out in 37 h.

recovered: in the case of (R_a)-**2b**, the starting carbonate was recovered with 78% ee, indicating some level of kinetic resolution.



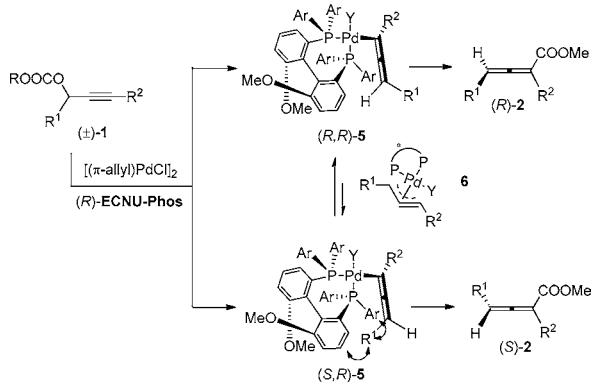
As discussed at the beginning, these 2,3-allenoates are quite useful in asymmetric synthesis (Scheme 3). For example, when (R_a)-**2f** was treated with 2 equiv of I_2 at −15 °C, the corresponding lactone (R)-**3** was obtained in 84% yield with 92% ee. The absolute configuration of (R)-**3** was established by X-ray diffraction study.[20] On the basis of this result and our previous studies,[14] we assigned the configuration of the 2,3-allenoate from (R)-**ECNU-Phos** as *R*. To date, there has not been an easy way to synthesize optically active primary 2,4-disubstituted 2,3-allenols,[21] which are also a type of versatile allenes for compounds with central or axial chirality.[22] Here, treating (R_a)-**2f** with DIBAL-H afforded allenol (R_a)-**4** in 64% yield with 93% ee.

Scheme 3. Applications of 2,3-Allenoate (R_a)-2f



A working model to predict the absolute configuration of the allene moiety for the highly enantioselective formation of (R_a)-**2** from racemic propargylic carbonates (±)-**1** is shown in Scheme 4. After oxidative addition of the (R)-**ECNU-Phos**-coordinated Pd catalyst with the starting material **1**, both (R)-and (S)-allenylpalladium species with **ECNU-Phos** would be generated. There should be an isomerization between these two diastereomers through $\sigma-\pi-\sigma$ rearrangement via the intermediacy of **6**.[23] Structural analysis showed that (S,R)-**5** is disfavored since there is an obvious steric interaction each of the R^1 group with the biaryl skeleton and the Ar group of (R)-**ECNU-Phos**, which does not exist for intermediate (R,R)-**5**. Thus, allenoate (R_a)-**2** is formed as the product in highly enantioselective fashion via the intermediacy of (R,R)-**5**.

Scheme 4. Prediction of the Absolute Configuration of the Product



In summary, we have realized for the first time the efficient formation of axial chirality spreading over three carbon atoms from readily available racemic propargylic carbonates bearing central chirality with high enantioselectivity. This reaction proceeds under 1 atm CO at room temprature with (R)- or (S)-**ECNU-Phos**, in which the 3,5-dimethoxy group may provide the required steric and electronic environment as well as the mild reaction temperature, which is critical for the temperature-sensitive nature of optically active allenes.[16] This study will surely stimulate interest in forming three-carbon axial chirality from all types of readily available racemic propargylic derivatives, providing the most convenient approach for the synthesis of chiral allenes with different functionalities for the

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further development of allene chemistry. Futher studies in this area are being pursued in this laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data, and NMR spectra of the products. 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.

■ ACKNOWLEDGMENTS

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(20) Crystal data for (*R*)-**3**: $C_{14}H_{15}IO_2$, MW = 342.16; triclinic, monoclinic, space group $P2(1)/n$; Mo Kα; final *R* indices [$I > 2\sigma(I)$]: R_1 = 0.0191, wR_2 = 0.0454; a = 8.378(2) Å, b = 9.574(3) Å, c = 17.660(5) Å, α = 90°, β = 90°, γ = 90°, V = 1416.5(6) Å^3, Z = 4; T = 296(2) K; 16292/2474 collected/unique reflns, R_{int} = 0.0223; 2363 observations [$I > 2\sigma(I)$], 154 parameters. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Centre as CCDC 935743.

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