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

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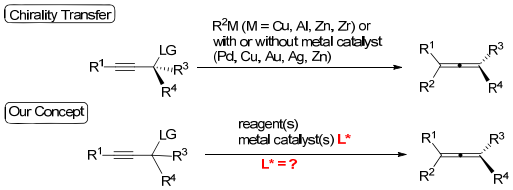
Supporting Information Placeholder

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 in fairly high ee. The combination of $[(\pi\text{-allyl})PdCl]_2$ with a new chiral bisphosphine ligand based on biphenyl skeleton ((*R*)-**ECNU-Phos**) 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 science of synthesis due to the fact that there are so many optically active naturally occurring 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 nickel-assisted coupling reaction;[4] however, the establishment of axial chirality of allenes, which spreads over three carbon atoms, is still a conundrum.[5,6]

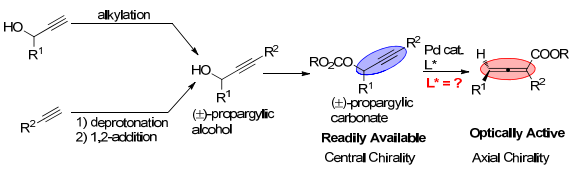
At the meantime, allenes have become more and more important due to the fact that many naturally occurring products with bio-potentials contain an allene unit;[7] they also serve as very important building blocks for organic synthesis;[8-10] (*S*)-2,4-bis(2-(bis(3,5-bis-(trifluoromethyl)phenyl)phosphino)phenyl)-5,5-dimethylhexa-2,3-diene had 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 are the chirality transfer from optically active propargylic derivatives with a proper leaving group.[12] However, in all these known cases, at least a stoichiometric amount of optically active starting compounds is required and racemization is in most cases a serious problem. We envisioned a catalytic system which may lead to highly optically active allenes from the readily available racemic propargylic derivatives.[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 vs racemic approach



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

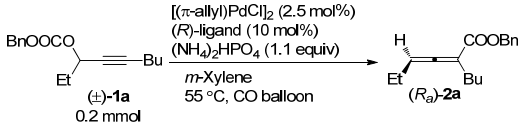
Scheme 2 Design of a Catalytic Approach to Synthesize Chiral 2,3-Allenoates



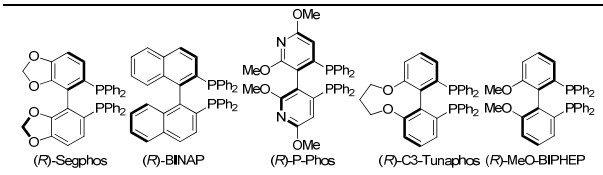
Based on our previous results with optically active propargylic mesylates using $Pd(dba)_2$ and (*S*)-Segphos as the catalyst with 1.1 equiv of $(NH_4)_2HPO_4$ as the base,[14] our initial experiments began with the carbonylation of racemic benzyl non-4-yn-3-yl carbonate (**1a**) under the catalysis of $Pd(dba)_2$ and (*R*)-Segphos. To our delight, when $[(\pi\text{-allyl})PdCl]_2$ was used, this reaction could occur at 55 °C to afford (R_a)-**2a** with 70% yield and 48% ee (Table 1, En-

try 1) (for screening of different Pd catalysts, see Table S1 in Supplementary Materials). Based on this result, we identified that bisphosphine ligands are the best skeletons among so many well-established chiral ligands (for some typical results with other ligands, see Table S2 in Supplementary Materials).[3] Then, some of the commercially available chiral diphosphine ligands were examined.[17] (*R*)-BINAP gave a better result (66% yield and 65% ee), but the ligand based on the bipyridyl skeleton, i.e., (*R*)-P-Phos, only led to 21% ee (Table 1, Entries 2 and 3); when (*R*)-C3-Tunaphos was used, (R_a)-**2a** could only be prepared with 44% yield and 63% ee (Table 1, Entry 4); interestingly, higher enantioselectivity was observed with the rather simple (*R*)-MeO-BIPHEP (Table 1, Entry 5).

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



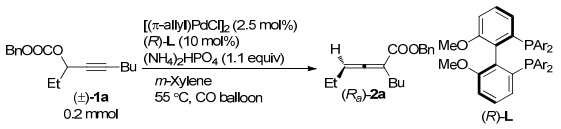
Entry	Ligand	Time (h)	Yield (%) of (R_a)-**2a** [a]	**1a** (%)[b]
1	(*R*)-Segphos	9	70 (48)	3
2	(*R*)-BINAP	5	66 (65)	16
3	(*R*)-P-Phos	5	49 (21)	28
4	(*R*)-C3-TunaPhos	5	44 (63)	43
5	(*R*)-MeO-BIPHEP	4	61 (71)	18



[a] Isolated yield, the ee value of **2a** was shown in parenthesis. [b] Determined by ^{1}H NMR using 1,3,5-trimethylbenzene as the internal standard.

With the results of (*R*)-MeO-BIPHEP in hand, we started to identify the best phenyl-substituent of the coordinating phosphorus center with the purpose of tuning its electronic and steric nature for a practical enantioselectivity:[18] no reaction occurred with the 2-furyl ligand ((*R*)-**L1**) (Table 2, Entry 1); When the 4-position of phenyl was substituted by methyl ((*R*)-**L2**), the yield was improved but ee dropped slightly (Table 2, Entry 2); 3,5-dimethyl phenyl ligand ((*R*)-**L3**) made both yield and ee drop sharply (Table 2, 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 of 3,5-positions by replacing Me with *t*-Bu ((*S*)-**L4**) led to a higher ee (Table 2, Entry 4); further introducing a 4-OMe to the aryl group of (*S*)-**L4** makes (*R*)-**L5**, which improved the enantioselectivity further, albeit slightly (Table 2, Entry 5). Interestingly, removing the 3,5-di-*t*-butyl groups from (*R*)-**L5**, i.e., (*R*)-**L6**, provided very comparable results: 48% yield and 63% ee of (R_a)-**2a** (Table 2, Entry 6); at the point of nowhere, it was observed that when relocating the methoxy group from 4-position to 3-position of the phenyl ring ((*R*)-**L7**), the rate of the reaction was increased together with a remarkable enantioselectivity: 57% of 2,3-allenoate with 79% ee (Table 2, Entry 7). Excitingly, extra introduction of a 5-OMe group ((*R*)-**L8**, abbreviated as **ECNU-Phos**) gave a much better result: 2,3-allenoate could be obtained with 51% yield/84% ee within 2 hours at 55 °C and 69% yield/83% ee after 7 hours of stirring at 45 °C (Table 2, Entries 8 and 9).[19] It is amazing to notice the difference between methyl and methoxy group (compare Entry 9 with Entry 3).

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



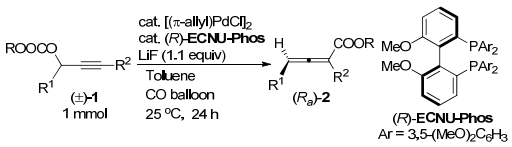
Entry	Ar ((*R*)-**L**)	t (h)	Yield of **2a** (%)[a]	**1a** (%)[b]
1	2-furyl (**L1**)[c]	5	0	97
2	4-MeC_6H_4 (**L2**)[c]	5	75 (69)	2
3	3,5-$Me_2C_6H_3$ (**L3**)[c]	5	58 (56)	5
4	3,5-(*t*-Bu)$_2C_6H_3$ (**L4**)[c,d]	5	47 (-60)	33
5	3,5-(*t*-Bu)$_2$-4-$MeOC_6H_2$ (**L5**)[c]	5	14 (66)	60
6	4-$MeOC_6H_4$ (**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

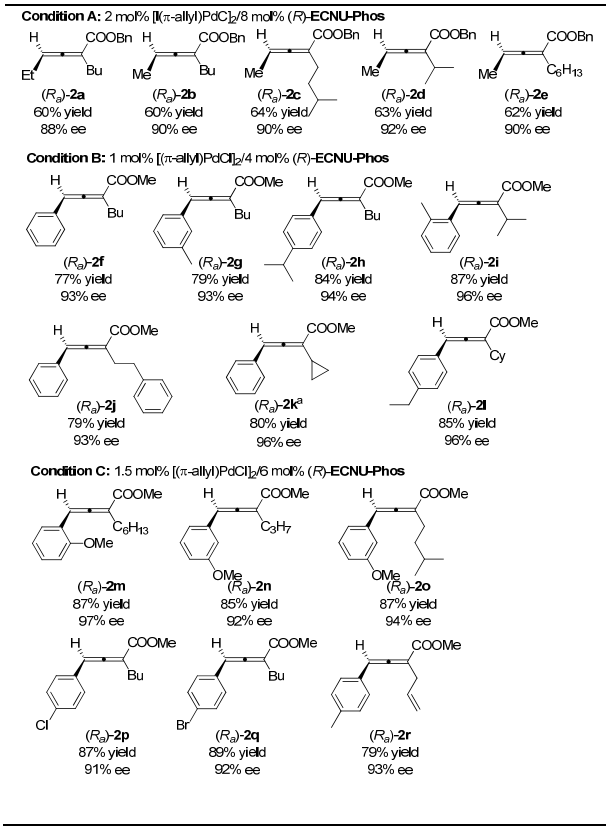
[a] Isolated yield, the ee value of **2a** was shown in parenthesis. [b] Determined by ^{1}H NMR using 1,3,5-trimethylbenzene as the internal standard. [c] The chiral ligands are bought from Stream Chemicals. [d] (*S*)-**L4** was used since only *S* isomer is commercially available. [e] Prepared according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

Moreover, base and solvent effects were also examined: LiF and toluene have been identified to be the best (for these results, see Tables S3 and S4 in Supplementary Materials). Thus, the scope of such an efficient strategy was explored by conducing the reaction of racemic propargylic carbonates, [(π-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 both R^1 and R^2 are alkyl groups, 2 mol% [(π-allyl)PdCl]$_2$ and 8 mol% of (*R*)-**ECNU-Phos** were required to afford 2,3-allenoates (R_a)-**2a**-(R_a)-**2e** with 60-64% yield and 88-92% ee after 24 h; interestingly, with R^1 being an aryl group, the reaction of methyl 1-phenyl-2-heptynyl carbonate (**1f**) could also proceed to afford the corresponding product (R_a)-**2f** at room temperature with an even higher enantioselectivity (93% ee) using only 1 mol% [(π-allyl)PdCl]$_2$ and 4 mol% of (*R*)-**ECNU-Phos**. As expected, (S_a)-**2f** could also be synthesized with the similar results by applying the enantiomer (*S*)-**ECNU-Phos** (78% yield and 94% ee) (eq. 1); in fact, this is quite general with R^1 being differently alkyl substituted aryl group: now R^2 may be alkyl ((R_a)-**2g**-(R_a)-**2i**), phenethyl ((R_a)-**2j**) and cycloalkyl groups ((R_a)-**2k** and (R_a)-**2l**); furthermore, when either electron-donating group (OMe) or electron-withdrawing group such as Cl and Br was introduced to the phenyl ring of R^1, 1.5 mol% [(π-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**) may also be accommodated. These versatile substituents such as OMe, Cl, Br, allyl will surely provide opportunities for further synthetic

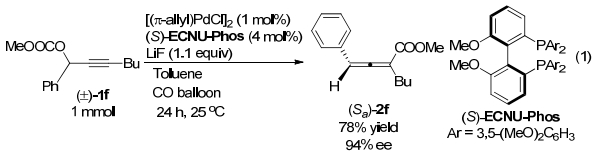
elaboration. It should be noted that in some cases some of the starting carbonate was recovered: in the case of (R_a)-**2b**, the starting carbonate was recovered in 78% ee, indicating some level of kinetic resolution.

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



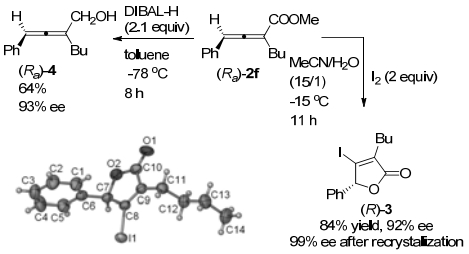


[a] The reaction was carried out in 37 hours.



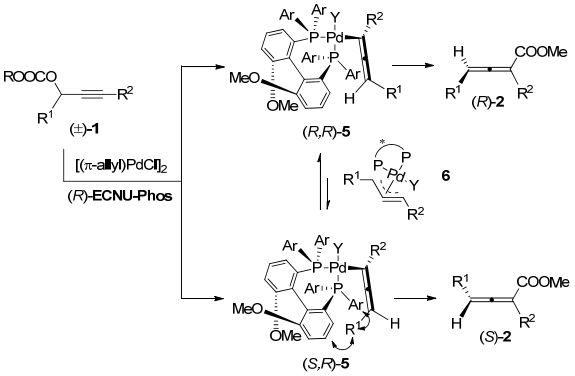
As discussed at the beginning, these 2,3-allenoates are quite useful in asymmetric synthesis (Scheme 3): when (R_a)-**2f** was treated with 2 equiv of I_2 at -15 °C, the corresponding lactone (*R*)-**3** was obtained in 84% yield with 92% ee. The absolute configuration of (*R*)-**3** was established by its X-ray diffraction study.[20] Based on this results and our previous studies,[14] we assigned the configuration of the 2,3-allenoate from (*R*)-**ECNU-Phos** as *R*. So far, there is no easy way for the synthesis of 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 the allenol (R_a)-**4** in 64% yield and 93% ee.

Scheme 3 Application 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 (*R*)-**ECNU-Phos** coordinated palladium catalyst with the starting material **1a**, both (*R*)-and (*S*)-allenyl palladium species with **ECNU-Phos** would be generated. There should be an isomerization between these two diastereomers through the σ-π-σ rearrangement via the intermediacy of **6**.[23] Based on the structural analysis, (*S,R*)-**5** is disfavored since there is obvious steric interactions between the R^1 group and the biaryl skeleton and an Ar group of (*R*)-**ECNU-Phos**, which does not exist in intermediate (*R,R*)-**5**. Thus, allenoate (*R*)-**2** is formed as the product highly enantioselectively via the intermediacy of (*R,R*)-**5**.

Scheme 4 Prediction of the absolute configuration of the products.



In summary, we have realized the efficient formation of such an axial chirality spreading over three carbon atoms from the readily available racemic propargylic carbonates bearing a central chirality with high enantioselectivity for the first time. This reaction proceeds under 1 atm of 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 the interest of forming the three-carbon axial chirality from all types of readily available different racemic propargylic derivatives providing the most convenient approach for the synthesis of chiral allenes with different functionalities for the further development of allene chemistry. Futher studies in this area are being pursued in this laboratry

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and 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 interests.

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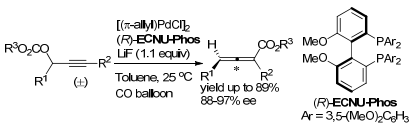
[(π-allyl)PdCl]2
(R)-ECNU-Phos
LiF (1.1 equiv)
Toluene, 25 °C
CO balloon
yield up to 89%
88-97% ee
(R)-ECNU-Phos
Ar = 3,5-(MeO)2-C6H3