ORGANIC CHEMISTRY FRONTIERS

RESEARCH ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Org. Chem. Front.*, 2024, **11**, 2477

Pd((*R*)-DTBM-SEGphos)Cl_2-catalyzed kinetic resolution of tertiary propargylic alcohols†

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Received 13th January 2024,
Accepted 28th February 2024

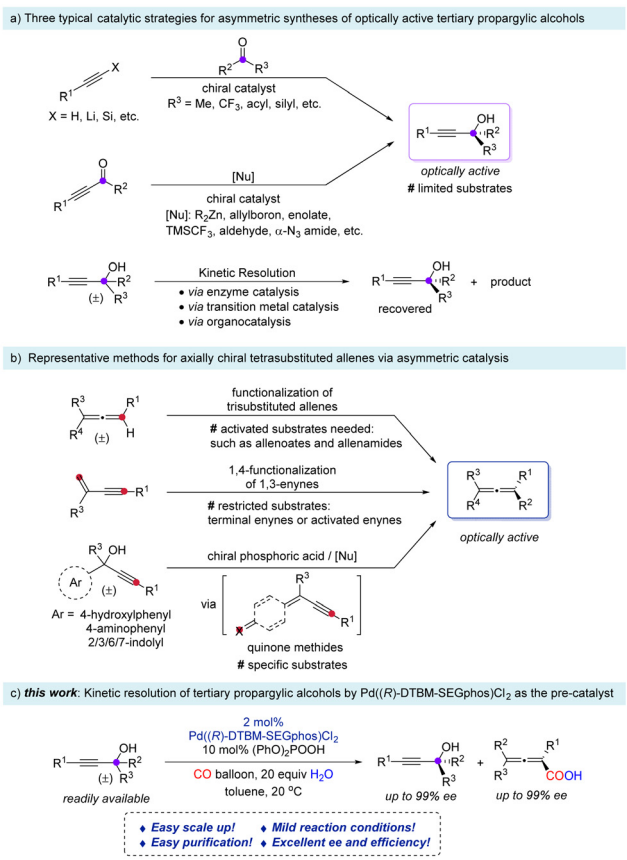
DOI: 10.1039/d4qo00082j

rsc.li/frontiers-organic

We report here an asymmetric carboxylation reaction based on kinetic resolution of tertiary propargylic alcohols by identifying Pd((*R*)-DTBM-SEGphos)Cl_2 as the pre-catalyst. A variety of optically active tertiary propargylic alcohols and tetrasubstituted 2,3-allenoic acids were obtained in good yields with excellent enantioselectivities. The salient features of this report include the use of readily available substrates, a readily available precatalyst, mild reaction conditions, remarkable functional group tolerance, gram-scale synthesis, and versatile synthetic transformations. Mass spectrometry experiments trapped some key intermediates, which revealed the mechanism.

Introduction

Optically active tertiary propargylic alcohols are useful building blocks in organic synthesis.[1] Typically, three catalytic strategies have been developed for asymmetric synthesis of tertiary propargylic alcohols (Scheme 1a):[2–6] (a) enantioselective alkynylation of methyl ketones,[2b,c,e,g,h] trifluoromethyl ketones,[3b–f] α-carbonyl ketones,[4] and acyl silanes[5] with terminal alkynes or 1-alkynyl trimethylsilanes[4b] in >90% ee; (b) enantioselective addition of nucleophiles (including Me_2Zn, Et_2Zn, $TMSCF_3$, aldehydes, α-N_3 amides, *etc.*) with 4-phenylbut-3-yn-2-one,[6a] pyridin-2-yl 1-alkynyl ketones,[6d] *tert*-butyl-substituted ethynyl ketones,[6e] propargylic ketoesters,[6f] or trifluoromethyl 1-alkynyl ketones[6g,h] in >90% ee; (c) catalytic kinetic resolution of racemic tertiary propargylic alcohols:[7] In 2019, Oestreich and coworkers reported the kinetic resolution by the enantioselective Si–O coupling catalyzed by MesCu/(*R*,*R*)-Ph-BPE affording tertiary 1-phenyl-1-(*n*-butyl)- or 1-cyclohexyl (or *N*-Boc-piperidinyl-4-yl)-1-methyl-2-alkynols in 92–96% ee;[7c] in 2021, Li and coworkers realized the kinetic resolution *via* chiral Rh(III)-catalyzed allenylation of benzamides affording tertiary 1-aryl-1-bulky alkyl (*tert*-butyl, adamantyl, cyclohexyl, isopropyl)-2-alkynols in >90% ee;[7d] in the same year, Zhou and coworkers demonstrated the kinetic resolution *via* Cu(I)-catalyzed azide–alkyne cycloaddition affording tertiary 1-aryl-1-bis(cyclohexyloxy)methyl (or fluoroalkyl)-2-alkynols in >90% ee.[7e] On the other hand, due to the axial allenes serving as versatile



Scheme 1 Approaches to optically active tertiary propargylic alcohols and tetrasubstituted allenes.

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†Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d4qo00082j

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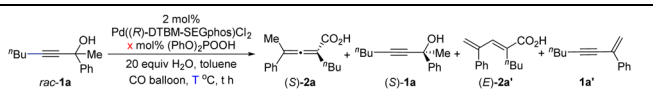
precursors in organic transformations and material science,[8] development of expeditious paths for constructing optically active tetrasubstituted allenes has been receiving increasing attention in the synthetic community. Representative catalytic methods for axially chiral tetrasubstituted allenes[9,10] are as follows (Scheme 1b): (a) direct asymmetric functionalization of trisubstituted allenes.[9f–i] These reported strategies are generally based on the formation of allenic carbanion analogues through the deprotonation of trisubstituted allenes to react with electrophiles, which demand the potential acidity of trisubstituted allenes such as trisubstituted allenoates and allenamides. (b) Asymmetric 1,4-functionalization of 1,3-enynes.[9j–o] It is restricted to terminal enynes or activated enynes. (c) Chiral phosphoric acid (CPA) catalyzed conjugate addition to quinone methides[9p–r] formed from specific substrates including 4-hydroxylphenyl, 4-aminophenyl, or 2/3/6/7-indolyl substituted propargylic alcohols. Therefore, catalytic asymmetric formation of tetrasubstituted allenes, especially from readily available chemicals, remains challenging. Recently, with the help of the supporting ligand PPh_3, we reported a Pd-catalyzed kinetic resolution carboxylation reaction of tertiary propargylic alcohols for a series of chiral 2,3-allenoic acids[11] and chiral tertiary propargylic alcohols[12] under different reaction conditions. Here we wish to report the identification of pre-prepared Pd((*R*)-DTBM-SEGphos)Cl_2 as the pre-catalyst, and both optically active tertiary propargylic alcohols and tetrasubstituted 2,3-allenoic acids could be easily accessed under mild reaction conditions with high efficiency and enantioselectivities *via* a kinetic resolution process. Furthermore, the synthetic potential of the current method has been showcased by scale-up reactions and derivatization reactions of optically active products.

Results and discussion

Optimization of reaction conditions

With Pd((*R*)-DTBM-SEGphos)Cl_2 as the pre-catalyst, the reactions of 2-phenyloct-3-yn-2-ol *rac*-**1a** were conducted and some of the typical results are shown in Table 1. First of all, two sets of control experiments were conducted by using Pd((*R*)-DTBM-SEGphos)Cl_2 as the catalyst instead of $PdCl_2$ and a chiral phosphine ligand under our previous optimal conditions (entries 1 and 2):[11,12] no products were observed at −5 °C (entry 1), and the reaction only delivered (*S*)-**2a** in 23% NMR yield at 25 °C (entry 2). Interestingly, the reaction exhibited a moderate efficiency at 15 °C and provided (*S*)-**2a** in 17% NMR yield with 93% ee in the absence of the supporting ligand, which suggested that the catalytic species involved in the current Pd-complex-catalyzed reaction may be different from that of the former protocols (entry 3). By prolonging the reaction time to 36 hours, the yield of (*S*)-**2a** was slightly improved with a higher yield of the enyne product (entry 4). To our delight, 44% yield of (*S*)-**1a** with 90% ee was observed when the reaction was carried out at 20 °C (entry 5). By applying 10 mol% of $(PhO)_2POOH$, the desired product (*S*)-**1a** was formed in 46% yield with 98% ee (entries 6–10). Thus, the optimal reaction conditions of this Pd((*R*)-DTBM-SEGphos)Cl_2-catalyzed kinetic resolution carboxylation reaction for the optically active tertiary propargylic alcohols have been identified as shown in entry 7 of Table 1. Under the same conditions, optically active tetrasubstitued 2,3-allenoic acid (*S*)-**2a** could also be smoothly obtained in 45% yield with 91% ee by just shortening the reaction time to 12 hours (entry 8).

Table 1 Optimization of reaction conditions[a]



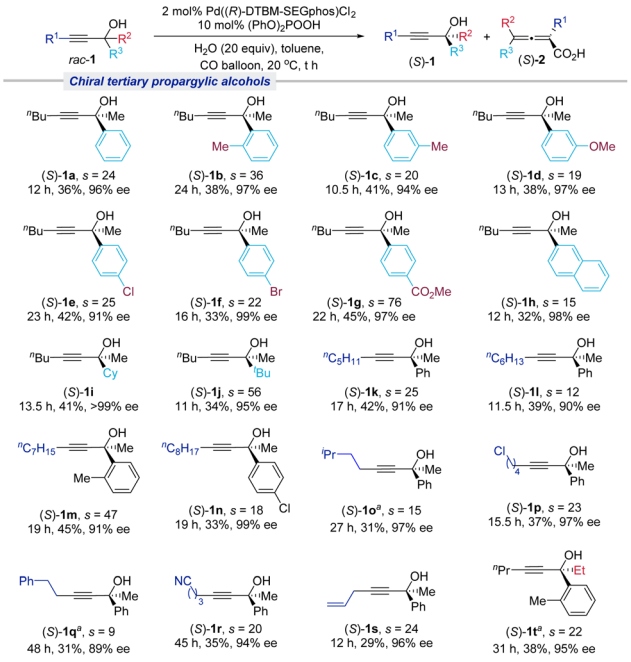
Entry	x	T (°C)	t (h)	(*S*)-**2a** Yield,[b] ee[c] (%)	(*S*)-**1a** Recovery,[b] ee[c] (%)	(*E*)-**2a′** Yield[b] (%)	**1a′** Yield[b] (%)
1[d]	20	−5	18	0, —	100, —	—	—
2[d]	2	25	18	23, 90	78, 30	—	—
3	20	15	18	17, 93	78, 16	—	5
4	20	15	36	20, 94	65, 19	—	13
5	20	20	18	51, 85	44, 90	2	4
6	15	20	18	51, 84	41, 93	2	4
7	10	20	18	51, 82	46, 98	2	2
8	10	20	12	45, 91	54, 70	—	—
9	5	20	18	55, 82	45, 96	—	—
10	2.5	20	18	51, 85	51, 91	—	—

[a] Reaction conditions: *rac*-**1a** (0.2 mmol), Pd((*R*)-DTBM-SEGphos)Cl_2 (2 mol%), $(PhO)_2POOH$ (x mol%), and H_2O (20 equiv.) in toluene (1 mL) at T °C with a CO balloon unless otherwise noted. [b] Determined by ^1H NMR analysis using dibromomethane as the internal standard. [c] Determined by HPLC analysis. [d] 20 mol% PPh_3 was added.

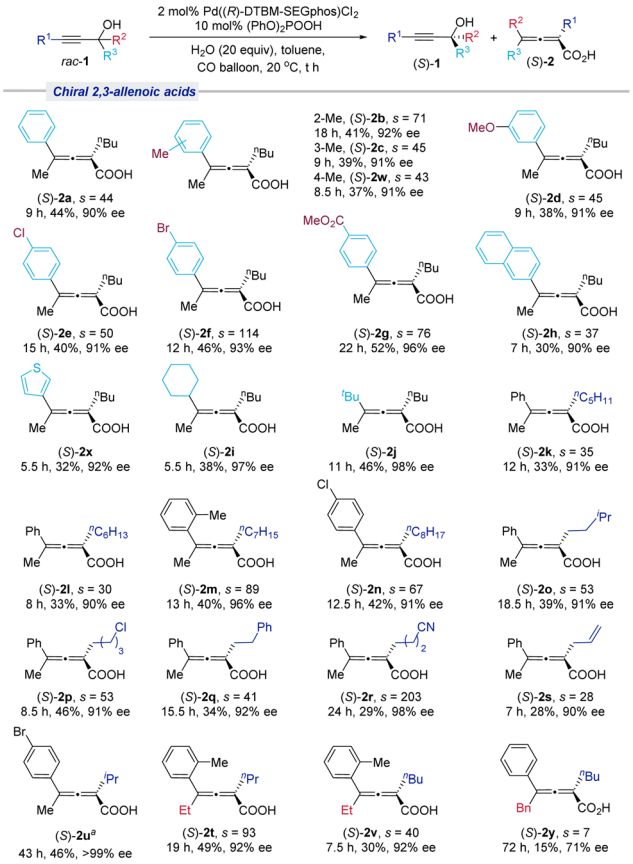
Substrate scope

With the optimized reaction conditions in hand, the generality of this Pd((*R*)-DTBM-SEGphos)Cl_2-catalyzed carboxylation reaction was investigated. As shown in Scheme 2, a range of tertiary propargylic alcohols containing electron-donating groups (**1b–1d**) or electron-withdrawing (**1e–1g**) on the phenyl ring furnished the corresponding products in good yields (33%–45%) with excellent ee (91%–99%). Naphthyl-substituted tertiary propargylic alcohol (**1h**) was compatible with the current system. Moreover, the substrates employing aliphatic substituents (Cy and ^{t}Bu) were also successfully resolved to afford the desired products (*S*)-**1i** and (*S*)-**1j** in good yields with excellent enantioselectivities. Besides ^{n}Bu substitution at the R^1 position, a series of tertiary propargylic alcohols containing different carbon chains ranging from C_3 to C_8 and versatile functional groups, such as the halogen atom (Cl), cyano, and allyl, were all suitable, affording the corresponding optically active tertiary propargylic alcohol products (*S*)-**1k**–(*S*)-**1s** in 29–45% yields with up to 99% ee. For the R^2 group, the methyl substituent may also be replaced with ethyl to recover (*S*)-**1t** in 38% yield with 95% ee.

Next, we turned our attention to the substrate scope for the formation of chiral 2,3-allenoic acids (Scheme 3). No obvious steric effect was observed since the substrates containing the



Scheme 2 The substrate scope of chiral tertiary propargylic alcohols. Reaction conditions: *rac*-**1** (0.5 mmol), Pd((*R*)-DTBM-SEGphos)Cl_2 (2 mol%), $(PhO)_2POOH$ (10 mol%), and H_2O (20 equiv.) in toluene (2.5 ml) at 20 °C with a CO balloon unless otherwise noted. *s* is the selectivity factor. $s = k_{fast}/k_{slow} = \ln[1 - (1 - \text{recovery})(1 + \text{ee})]/\ln[1 - (1 - \text{recovery})(1 - \text{ee})]$. Recovery is determined by ^{1}H NMR analysis, and ee is the enantiomeric excess value determined by HPLC analysis. [a] The reaction was carried out with 12 mol% $(PhO)_2POOH$.

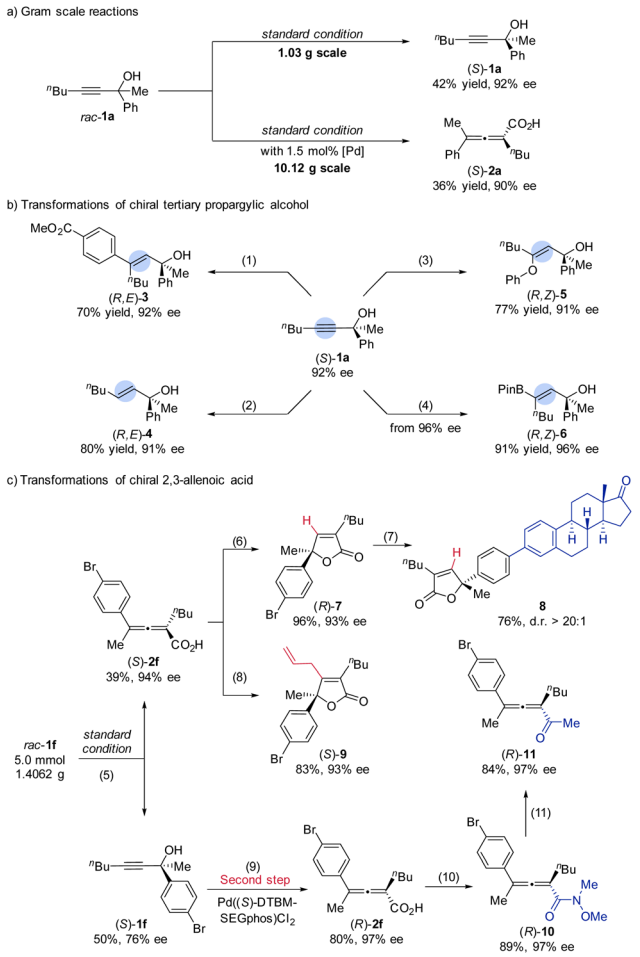


Scheme 3 The substrate scope of chiral 2,3-allenoic acids. Reaction conditions: *rac*-**1** (0.5 mmol), Pd((*R*)-DTBM-SEGphos)Cl_2 (2 mol%), $(PhO)_2POOH$ (10 mol%), and H_2O (20 equiv.) in toluene (2.5 ml) at 20 °C with a CO balloon unless otherwise noted. *s* is the selectivity factor. $s = k_{fast}/k_{slow} = \ln[1 - (1 - \text{recovery})(1 + \text{ee})]/\ln[1 - (1 - \text{recovery})(1 - \text{ee})]$. Yield is determined by ^{1}H NMR analysis, and ee is the enantiomeric excess value determined by HPLC analysis. [a] The reaction was carried out with 4 mol% Pd((*R*)-DTBM-SEGphos)Cl_2.

methyl group at the 2-, 3- or 4-position of the phenyl group provided the targeted products (*S*)-**2b**, (*S*)-**2c** and (*S*)-**2w** in good yields (37%–41%) with high ee (91%–92%). The substrates bearing the functional groups OMe, Cl, Br, and CO_2Me on the phenyl ring also underwent the carboxylation reaction efficiently, affording the corresponding products (*S*)-**2d**–(*S*)-**2g** in good yields with more than 90% ee. 2-Naphthyl substituted and 3-thienyl substituted propargylic alcohols were also well tolerated (**1h** and **1x**). Notably, the alkyl substituted substrates at R^3 could also be converted to the desired products (*S*)-**2i** and (*S*)-**2j** smoothly. R^1 with different carbon chains bearing a variety of different functional groups (halide, cyano, allyl) afforded the desired products (*S*)-**2k**–(*S*)-**2s** and (*S*)-**2u** in good yields with no less than 90% ee. Furthermore, when R^2 was an ethyl group, the reaction also formed the chiral 2,3-allenoic acids (*S*)-**2t** and (*S*)-**2v** with high enantioselectivities. However, when R^2 was Bn, the reaction was slow, affording 15% of (*S*)-**2y** with 71% ee after 72 hours.

Gram scale reactions and synthetic applications

A gram-scale carboxylation reaction worked smoothly, delivering the corresponding chiral product (*S*)-**1a** in 42% yield with 92% ee (Scheme 4a); the 50 mmol scale reaction of *rac*-**1a** afforded 4.24 g of (*S*)-**2a** in 36% isolated yield and 90% ee. To exhibit the synthetic utility, several transformations of (*S*)-**1a** have been carried out as shown in Scheme 4b: rhodium catalyzed highly regioselective hydroarylation of (*S*)-**1a** with boronic acid afforded the desired product (*R*,*E*)-**3** in good yields without erosion of ee;[13] the reaction of (*S*)-**1a** with red-Al afforded the allylic alcohol (*R*,*E*)-**4** in 80% yield with 91% ee;[14] (*S*)-**1a** could be selectively transformed to phenyl enol ether (*R*, *Z*)-**5** in 77% yield with 91% ee under gold catalysis.[15] Moreover, the copper-catalyzed hydroboration of (*S*)-**1a** delivered the useful intermediate (*R*,*Z*)-**6** in 91% yield.[16] On the other hand, 1.4 g of *rac*-**1f** was smoothly converted to (*S*)-**2f** in 39% yield with 94% ee and 50% of (*S*)-**1f** was recovered in 76% ee under the standard conditions (Scheme 4c). Subsequently, a successful successive kinetic resolution of the recovered (*S*)-**1f** to afford (*R*)-**2f** in higher yield (80%) and ee (97%) was realized with Pd((*S*)-DTBM-SEGphos)Cl_2. Employing this pair of enantiomeric allenoic acids (*S*)-**2f** and (*R*)-**2f**, a series of transformations were investigated. A CuCl-catalyzed cycloisomerization reaction was realized affording (*R*)-**7** in excellent yield without the loss of ee.[17] Furthermore, a Suzuki coupling reaction with the estrone-derived boronic acid afforded **8** in good yield and dr (>20 : 1).[18] A cyclization reaction of (*S*)-**2f** catalyzed by $PdCl_2$

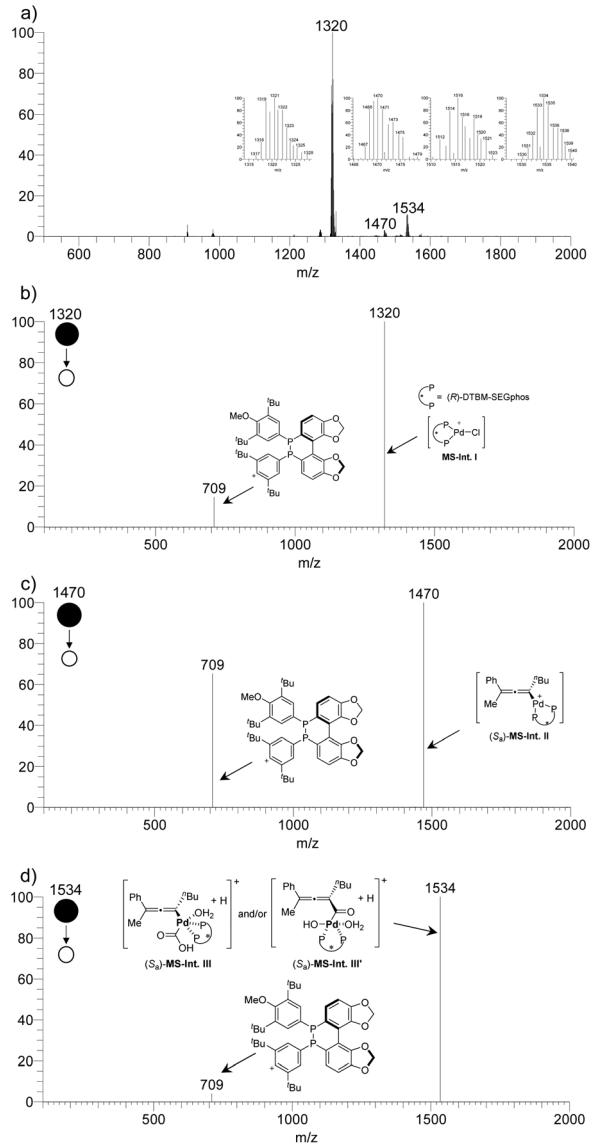


Scheme 4 The gram scale reactions and synthetic applications. Reaction conditions: (1) $(Cp^*RhCl_2)_2$ (2.5 mol%), $(4\text{-}MeO_2C)C_6H_4B(OH)_2$ (2.0 equiv.), $AgBF_4$ (15 mol%), NaOAc (20 mol%), MeOH, rt, air, 12 h; (2) red-Al (3.5 equiv.), Et_2O, −78 °C, 1 min, rt, 6 h; (3) PPh_3AuNTf_2 (2 mol%), PhOH (1.2 equiv.), K_2CO_3 (1.0 equiv.), $CHCl_3$, 50 °C, 16 h; (4) B_2Pin_2 (1.3 equiv.), CuCl (15 mol%), PCy_3 (18 mol%), NaO^tBu (15 mol%), MeOH (2.0 equiv.), toluene, rt, 12 h; (5) *rac*-**1f** (5.0 mmol), Pd((*R*)-DTBM-SEGphos)Cl_2 (2 mol%), $(PhO)_2POOH$ (10 mol%), H_2O (20 equiv.), toluene, CO balloon, 20 °C, 11 h; (6) CuCl (4 mol%), MeOH, 60 °C, 1 h; (7) Pd(dppf)Cl_2 (10 mol%), boronic acid (1.1 equiv.), K_2CO_3 (2.0 equiv.), DMSO, 80 °C, 1.5 h; (8) $PdCl_2$ (5 mol%), allyl bromide (6 equiv.), DMA, 50 °C, 18 h; (9) Pd((*S*)-DTBM-SEGphos)Cl_2 (2 mol%), $(PhO)_2POOH$ (10 mol%), H_2O (20 equiv.), toluene, CO balloon, 20 °C, 16 h; (10) methyl methoxylamine hydrochloride (1.3 equiv.), EDC·HCl (1.3 equiv.), NEt_3 (1.3 equiv.), DMAP (0.1 equiv.), DCM, 0 °C to rt, 3 h; (11) MeMgBr (4.0 equiv.), THF, −78 °C to 0 °C, 1 h.

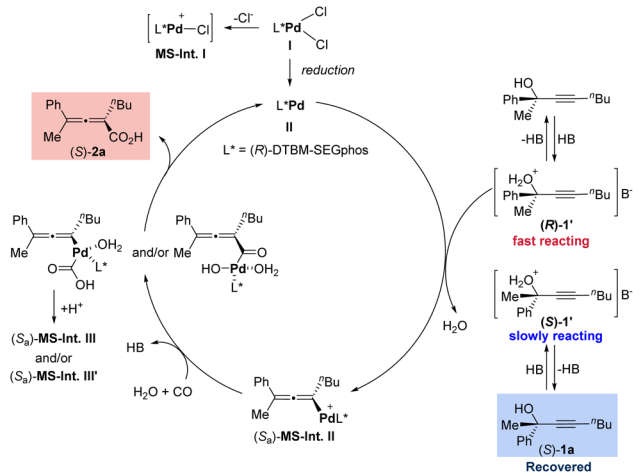
in the presence of allyl bromide afforded allyl furanone (*S*)-**9** in 83% yield with 93% ee.[19] The reaction of (*R*)-**2f** with methyl methoxylamine hydrochloride led to the formation of Weinreb amide (*R*)-**10** in 89% yield with 97% ee.[20] In addition, the treatment of (*R*)-**10** with MeMgBr could afford chiral allenone (*R*)-**11** in 84% yield and with 97% ee.

SAESI-MS studies

To further reveal the process of this Pd((*R*)-DTBM-SEGphos)Cl_2-catalyzed reaction, solvent-assisted electrospray ionization mass spectrometry (SAESI-MS) studies were carried out (Scheme 5).[21] Under standard conditions, the resulting mixture was analyzed after stirring for 10 min. A signal at *m*/*z* 1320 was observed, which matched the *m*/*z* of the intermediate $[Pd((R)\text{-DTBM-SEGphos})Cl]^+$ (calcd for $C_{74}H_{100}{}^{35}ClO_8P_2{}^{106}Pd^+$: 1319.5611) **MS-Int. I** (Scheme 5b). The reaction of the catalyst with the H^+-activated tertiary propargylic alcohols, H_2O, and CO could afford the allenylpalladium intermediate (S_a)-**MS-Int. II** (Scheme 5c, *m*/*z* 1470). Moreover, the carboxylation inter-



Scheme 5 The SAESI-MS studies. (a) SAESI-MS spectrum of the reaction solution after stirring for 10 min; the inset SAESI-MS spectrum shows the major signal from *m*/*z* 1315 to 1330, 1465 to 1480, 1510 to 1525 and 1525 to 1540; (b) SAESI-MS/MS spectrum of the complex ion $[Pd((R)\text{-DTBM-SEGphos})Cl]^+$ (**MS-Int. I**) at *m*/*z* 1320; (c) SAESI-MS/MS spectrum of the complex ion (S_a)-**MS-Int. II** at *m*/*z* 1470; (d) SAESI-MS/MS spectrum of the complex ion (S_a)-**MS-Int. III** and/or (S_a)-**MS-Int. III'** at *m*/*z* 1534.



Scheme 6 The proposed mechanism.

mediate (S_a)-**MS-Int. III** and/or (S_a)-**MS-Int. III′** (Scheme 5d, *m*/*z* 1534) was also detected.

Combining the ^{1}H NMR monitoring experiment (for details see ESI Table 1†) and mass spectrometric studies, a catalytic cycle was proposed as shown in Scheme 6. First, Pd((*R*)-DTBM-SEGphos)Cl_2 **I** would be reduced *in situ* to form the catalytically active species Pd(0)((*R*)-DTBM-SEGphos) **II**. Then **II** would react with the configuration-matched H^+-activated propargylic alcohol (*R*)-**1′** to afford the allenylpalladium intermediate (S_a)-**MS-Int. II** *via* stereo-defined *anti*-S_N2'-type oxidative addition. The subsequent reaction of (S_a)-**MS-Int. II** with CO and H_2O delivered the carboxylation intermediate (S_a)-**MS-Int. III** and/or (S_a)-**MS-Int. III′**, which generated the product 2,3-allenoic acid (*S*)-**2a** *via* reductive elimination. Moreover, the slowly reacting propargylic alcohol (*S*)-**1a** could be recovered in excellent ee.

Conclusions

In summary, a Pd((*R*)-DTBM-SEGphos)Cl_2-catalyzed carboxylative kinetic resolution reaction of racemic tertiary propargylic alcohols has been developed. Under this set of mild reaction conditions, a variety of enantioenriched tertiary propargylic alcohols and optically active tetrasubstituted 2,3-allenoic acids were obtained in good yields with excellent ee (up to >99%). Gram-scale reactions were easily realized and the optically active tertiary propargylic alcohols and 2,3-allenoic acids could be converted to a series of optically active functionalized products indicating the generality and practicality of this strategy. Mass spectrometry experiments revealed the catalytic process. Further studies in this topic are currently underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Financial support from the National Key R&D Program of China (2022YFA1503200 for S. M.), the National Natural Science Foundation of China (21988101 for S. M. and 22171048 for H. Q.), and the Shanghai Rising-Star Program (23QA1400400 for H. Q.) is greatly appreciated. We thank Dr Yizhan Zhai in this group for reproducing the results of (*S*)-**1h**, (*S*)-**1j** and (*S*)-**2l**, presented in Schemes 2 and 3.

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