Communication

Regio- and Enantioselective Allylic Alkylation of Terminal Alkynes by Synergistic Rh/Cu Catalysis

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Regio- and Enantioselective Allylic Alkylation of Terminal Alkynes by Synergistic Rh/Cu Catalysis

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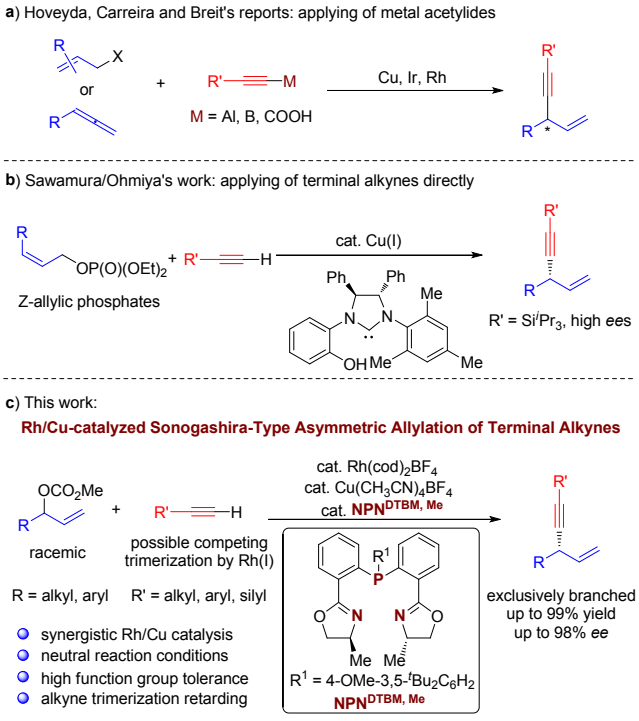
Supporting Information Placeholder

ABSTRACT: A highly branch- and enantioselective 1,4-enynes synthesis from readily available terminal alkynes and racemic allylic carbonates by Sonogashira type synergistic Rh and Cu catalysis under neutral conditions has been developed. Aliphatic and aromatic terminal alkynes with various functional groups could be used directly. An inner-sphere reductive elimination C(sp)-C(sp^3) bond formation mechanism is supported by the stoichiometric reaction.

Transition-metal-catalyzed asymmetric allylic substitutions (AAS) provide powerful methods for enantioselective construction of carbon-carbon bonds.[1] Various soft or hard carbon nucleophiles have been successfully utilized. Terminal alkynes are also potential nucleophiles to prepare the 1,4-enynes products, which are versatile building blocks in organic synthesis for the easy functional group manipulation on the double and triple bonds.[2] However, the AAS reaction from terminal alkynes is underdeveloped probably due to the diverse reactivities of alkynes in the presence of some commonly used AAS transition metals (Pd, Ir and Rh).[3] Hoveyda reported the first asymmetric allylic alkynylation by using alkynylaluminum reagents in the presence of Cu catalyst.[4] Carreira[5] and Breit[6] successfully realized the synthesis of highly enantio-enriched 1,4-enynes from alkynylboron and alkynyl carboxylic acid respectively (Scheme 1, **a**).[7] Direct asymmetric allylation of readily available terminal alkynes under mild condition is challenging and rewarding in terms of atom- and step-economy. Only two examples have been reported. A significant progress has been made by Sawamura and Ohmiya in Cu-catalyzed asymmetric allylic alkylation of terminal alkynes with (*Z*)-allylic phosphates (Scheme 1, **b**).[8a] High enantioselectivities were observed for triisopropylsilylacetylene and other bulky alkynes. The enantio-selectivities for the reactions of aryl or aliphatic terminal alkynes are still moderate. Tan and Lee reported Cu/guanidine-catalyzed enantioselective allylic alkynylation of cyclic allylic bromide under biphasic condition.[8c] A highly regio- and enantioselective direct coupling of functionalized terminal alkynes and easily available unsymmetrical allylic precursors under neutral conditions is still in demand.[9]

Rhodium has be reported to catalyze the highly branch-selective allylic alkylation reactions from monosubstituted allylic substrates.[10] We recently developed the Rh(I)/bisoxazoline-phosphine-catalyzed regio- and enantioselective allylic substitution of different nitrogen, carbon, oxygen and sulfur pronucleophiles under neutral conditions, in which challenging alkyl-group-bearing branched racemic and linear (*Z* and *E*) allylic substrates were converted to the same chiral products.[11] The released carbonate or the methoxide anion acts as the base to deprotonate the acidic pronucleophiles. The less acidic C(sp)-H bond and the competing Rh(I)-catalyzed terminal alkyne dimer- or trimerization are the main obstacles to expand the scope of pronucleophiles to terminal alkynes. Inspired by the activation of terminal alkynes with Cu in the Sonogashira coupling reaction, we envisioned that the addition of catalytic amount of copper salt is able to help enhance the acidity of terminal alkynes. The Cu acetylide formation and subsequent transmetalation to Rh may lead to the production of skipped enynes. Herein, we report a highly branch- and enantioselective allylic alkylation of a variety of functionalized aryl, aliphatic and silyl alkynes by synergistic Rh and Cu catalysis with challenging racemic allylic carbonates under neutral conditions (Scheme 1, **c**).[12]

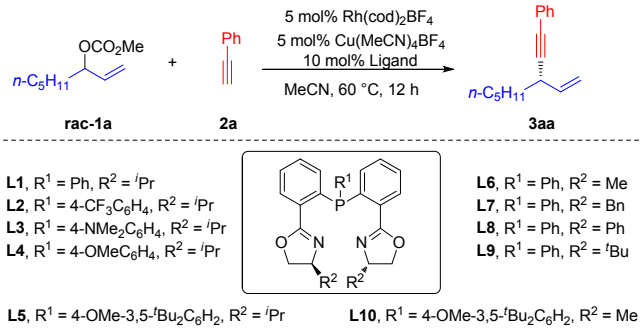
Scheme 1. Transition-Metal-Catalyzed Asymmetric Allylic Alkynylation to Chiral 1,4-Enynes



Allylic carbonate *rac*-**1a** and phenylacetylene **2a** were chosen as the model substrates (Table 1). With **L1** (10 mol%), skipped enyne **3aa** was isolated in 63% yield and 91% *ee* in the presence 5 mol% $Rh(cod)_2BF_4$ and 5 mol% $Cu(CH_3CN)_4BF_4$ in acetonitrile at 60 °C (entry 1), along with 7% benzene derivatives byproducts from Rh-catalyzed alkyne trimerization.[13] The use of coordinating

acetonitrile as solvent is essential for the high yields. Reactions in other solvents lead to the faster consumption of alkynes by trimerization and low yields of **3aa** (see SI). 36% yield and 72% *ee* were obtained in the control experiment without $Cu(CH_3CN)_4BF_4$ and the corresponding ligand, which indicates the important role of Cu (entry 2). The yield dropped to 8% when 5 mol% $Rh(cod)_2BF_4$, $Cu(CH_3CN)_4BF_4$ and **L1** were used respectively (entry 3). A competition between Rh(I) and Cu(I) to coordinate with **L1** may exist. The reaction doesn't proceed with only Cu catalyst (entry 4). To accelerate the reaction rate of allylic substitutions, we then modified the electronic and steric nature of the ligands. Catalysts with electron-rich aromatic rings at R^1 make the reaction more reactive and 77% of **3aa** was observed when ligands with 4-NMe_2 and 4-MeO groups were used (entries 6, 7). Full conversion of **1a** was realized with the 3,5-di-t-butyl-4-$MeOC_6H_2$ (DTBM) group-substituted ligand **L5** (entry 8). The substituents on the oxazoline rings have significant influence on the effect of the ligands. Compared to **L1**, **L6** and **L7** with smaller methyl and benzyl groups at R^2 are more effective (entries 9 and 10), while **L8** and **L9** with bulkier phenyl and *t*-butyl groups give low conversions and enantioselectivies (entries 11 and 12). As expected, **L10** with

Table 1. Optimization for Rh/Cu-Catalyzed Asymmetric Allylic Alkylation of Terminal Alkynes[a]

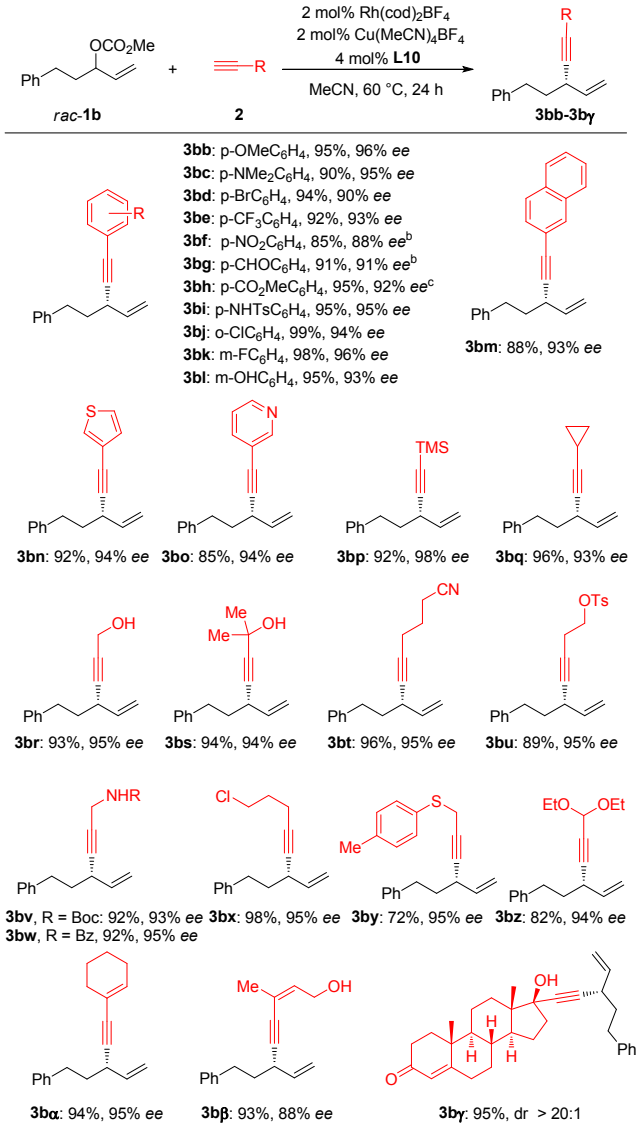


entry	ligand	yield (%)[b]	*ee* (%)[c]
1	**L1**	63	91
2[d]	**L1**	36	72
3[e]	**L1**	8	90
4[f]	**L1**	< 5	--
5	**L2**	62	91
6	**L3**	77	92
7	**L4**	77	91
8	**L5**	99	92
9	**L6**	97	91
10	**L7**	88	92
11	**L8**	29	85
12	**L9**	11	58
13	**L10**	99	90
14[g]	**L5**	80[h]	90
15[g]	**L10**	95[h]	90

[a]Conditions: **1a** (0.5 mmol), **2a** (0.75 mmol) in CH_3CN (0.5 mL). [b]Determined by ^1H NMR integration relative to 1,3,5-trimethylbenzene. [c]The *ee* was determined by HPLC with a chiral column. [d]Cu(I) was not added and 5 mol% **L1** was used. [e]5 mol% Rh(I), 5 mol% Cu(I) and 5 mol% **L1** were used. [f]Rh(I) was not added and 5 mol% **L1** was used. [g]$Rh(cod)_2BF_4$ (2 mol%), $Cu(CH_3CN)_4BF_4$ (2 mol%) and 4 mol% **L10** in 24 h. [h]Isolate yield.

DTBM and Me group leads to the full conversion (entry 13). The reaction efficiency with **L10** remains when reducing the catalyst loading to 2 mol% and expanding the time to 24 h (entry 15), while lower yield was obtained when **L5** was used at lower catalyst loading (entry 14). Various achiral ligands for Cu were examined since chiral ligand is unnecessary for Cu. Nevertheless, no ligand is superior than **L10** in controlling both reactivity and enantioselectivity, probably due to the ligand exchange between Rh and Cu or the slow transmetalation (see SI).[14]

Scheme 2. Scope of Alkynes[a]

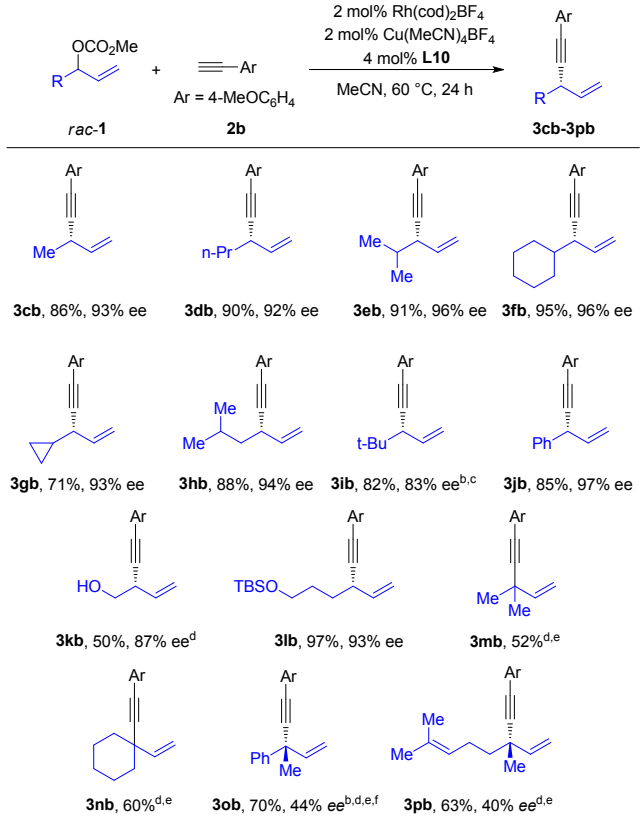


[a]Condition: **1b** (0.5 mmol, 1.0 equiv), **2** (0.75 mmol, 1.5 equiv) in 0.5 mL CH_3CN. [b]48 h. [c]3 mol% Rh(I)/Cu(I) and 6 mol% **L10** at 80 °C.

With the optimized condition in hand, we firstly evaluated the scope of terminal alkynes (Scheme 2). With the *rac*-**1b** as the model allylic carbonate, various alkynes successfully undergo the allylic alkylation reactions. Electron-donating and moderately electron-withdrawing groups in the aryl alkynes have neglectable effect on yields and *ee*s (**3bb** to **3be**). However, strong electron-withdrawing nitro group makes the reaction slow at the standard condition. The yield was improved to 85% when the reaction was conducted at 80 °C with slightly lower *ee* (**3bf**). Aldehyde, ester, free sulfonamide and hydroxyl groups can be tolerated (**3bg** to **3bi**, **3bl**). The ortho- and meta-substituted aryl alkynes can also be transformed to

products smoothly (**3bj** to **3bl**). Other aromatic rings, such as 2-naphthyl, 3-thiophenyl and 3-pyridyl groups, can also be introduced to give 1,4-enynes **3bm** to **3bo**. Silyl-containing **3bp** was prepared in high yield and *ee* from trimethylsilylacetylene **2p**, which allows further deprotection to prepare chiral terminal alkyne. Aliphatic alkynes with different functional groups were also utilized in this transformation. Free propargyl alcohols react selectively at the C-H bond and no allylic ethers were detected (**3br** and **3bs**). Cyano, p-toluenesulfonate, amides, chloride and sulfide were all tolerated under this mild condition (**3bt** to **3by**). Acetal-containing **3bz** was synthesized in high yield, which could be converted to the aldehyde. 1,3-Enynes readily react to afford the dienynes **3bα** and **3bβ**. The highly diastereoselective formation of **3bγ** from ethisterone indicates this method can be used in late-stage functionalization of complex molecules. The absolute configurations of **3bp** and **3bα** were assigned to be *S* by comparing with literature.[8a]

Scheme 3. Scope of Allylic Carbonates[a]

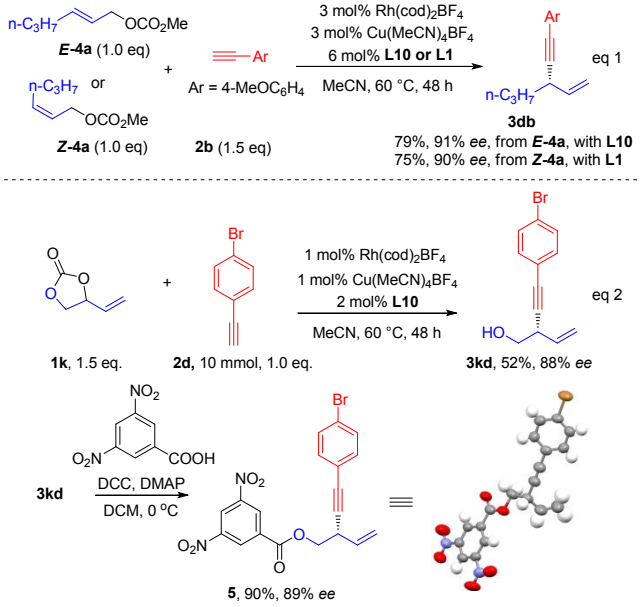


[a]Conditions: **1** (0.5 mmol, 1.0 equiv) and **2b** (0.75 mmol, 1.5 equiv) in CH_3CN (0.5 mL). [b]48 h. [c]3 mol% Rh(I)/Cu and 6 mol% **L10** were used. [d]**1** (0.75 mmol, 1.5 equiv) and **2b** (0.5 mmol, 1.0 equiv). [e]5 mol% Rh(I)/Cu and 10 mol% **L10**. [f]t-Butyl carbonate was used instead of methyl carbonate.

The scope of allylic carbonates was then examined with alkyne **2b** as model substrate (Scheme 3). Simple methyl and n-propyl substituted chiral 1,4-enynes **3cb** and **3db** were synthesized routinely under the standard condition. Sterically more hindered α- and β-branched allylic carbonates with isopropyl, cyclopropyl, cyclohexyl and isobutyl groups reacted smoothly to afford the corresponding skipped enynes in high yields and enantioselectivities (**3eb** to **3hb**). The challenging *t*-butyl group was also introduced to 1,4-enynes, although the *ee* is slightly lower (**3ib**). Phenyl substituted allylic carbonate **1j** also participated in this reaction to generate **3jb** in 85% yield and 97% *ee*. The absolute configuration of **3jb** was assigned to be *R* by comparing with literature.[5] **3kb** and **3lb** with free or protected hydroxyl groups were obtained with high *ee*s. Tertiary allylic carbonates can also be applied in this transformation to build 1,4-enynes with quaternary carbon centers in moderate yields (**3mb** to **3pb**) and *ee*s (**3ob** and **3pb**) under the standard condition.

As predicted, *Z*- and *E*-linear allylic methyl carbonates (***Z*-4a** and ***E*-4a**) underwent this asymmetric allylic alkylation of terminal alkyne **2b** to afford **3db** (eq 1, Scheme 4). However, these reactions were slower than the reaction of branched substrate **1d**. 3 mol% catalysts and longer time (48 h) are necessary to get high yields. The same level of enantioselectivities were observed from three different allylic precursors. The asymmetric allylic alkylation of terminal alkynes can be conducted in 10 mmol scale. **3kd** can be prepared in 52% yield and 88% *ee* in the presence of 1 mol% catalyst after 48 hours (eq 2). After protection with 3,5-dinitrobenzoic acid, a solid **5** was isolated and the *S* absolute configuration was further confirmed by single crystal X-ray diffraction analysis.

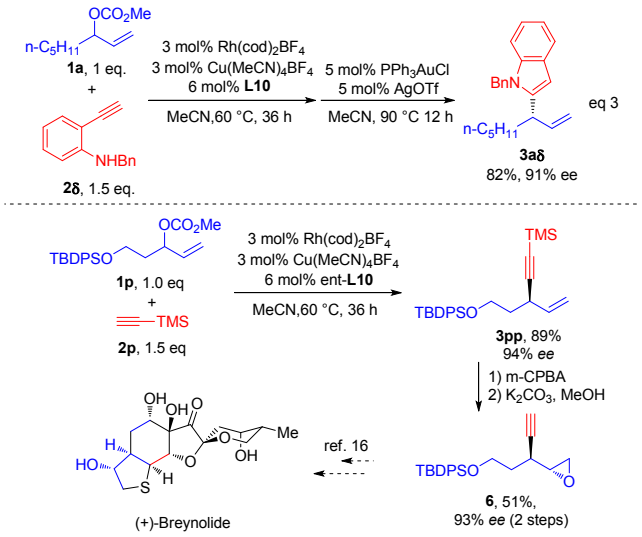
Scheme 4. Reactions of Linear Allylic Carbonates and Absolute Configuration Assignment



N-Benzyl-2-ethynylaniline **2δ** reacted at the terminal alkyne site selectively and chiral N-benzyl-2-allylindole[15] **3aδ** was isolated in 82% yield and 91% *ee* after the gold-catalyzed cyclization (eq 3, Scheme 5). This method was also utilized to synthesize **3pp** in the presence of *ent*-**L10**, which could be transformed to compound **6** as the key fragment in the synthesis of (+)-Breynolide.[16]

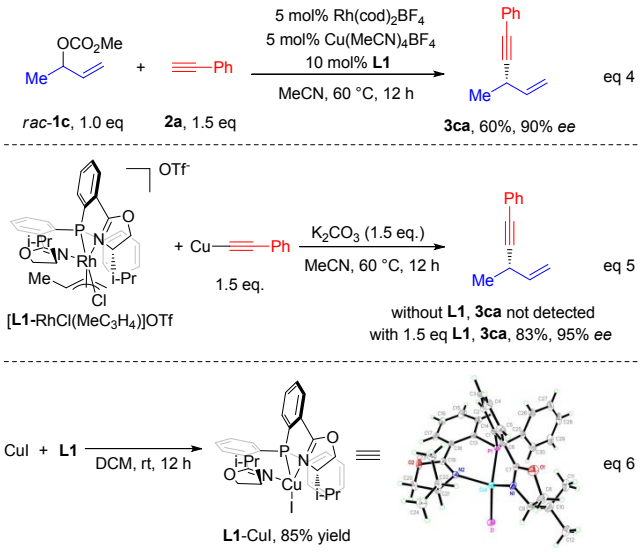
To gain mechanistic insight of the Rh/Cu-catalyzed asymmetric allylic alkylation of terminal alkynes, control and stoichiometric reactions were conducted (Scheme 6). **3ca** was isolated in 60% yield and 90% *ee* under the catalysis of Rh/Cu and **L1** (eq 4). The stoichiometric reaction of previously reported [**L1**-RhCl(MeC_3H_4)]OTf with Cu-acetylide in the presence of K_2CO_3 gives no trace of **3ca**. The addition of 1.5 eq of **L1** leads to the isolation of **3ca** in 83% yield and 95% *ee* (eq 5). This result is consistent with the fact that extra ligand for Cu is mandatory for high conversions. The addition **L1** may break the Cu acetylide oligomers and generate the key Cu-**L1** acetylide. Complex **L1**-CuI

Scheme 5. The Synthesis of Chiral 2-Allylindole and the Fragment of (+)-Breynolide



with distorted tetrahedral geometry was synthesized in high yield when CuI and **L1** were mixed in DCM (eq 6). A linear relationship between the *ee* values of the product and ligand indicates that no metal complex with two chiral ligands is involved in the catalysis (see SI). The C-C bond formation step is different from the previously proposed outer-sphere addition of nitrogen and other nucleophiles.[11a] A mechanism involving the transmetalation of Cu-acetylide to rhodium complex and subsequent reductive elimination is more likely based on the observed absolute configuration of product **3bp, 3bα**, **3jb**, **3ca** and crystalized **5**.[17,18] The high exo/endo selectivity in [**L1**-RhCl(MeC$_3$H$_4$)]OTf complex leads to the excellent enantioselectivity.

Scheme 6. Mechanism Studies



In summary, we developed a highly branch- and enantioselective allylic alkylation of terminal alkynes by synergistic Rh and Cu catalysis. Chiral 1,4-enynes were synthesized from a variety of readily available terminal alkynes with different functional groups and racemic allylic carbonates under neutral conditions. The challenging alkyne trimerization by Rh(I) could be retarded by the applying of acetonitrile solvent. Mechanism studies support the inner-sphere reductive elimination C-C bond formation process, which encourages us to explore the Rh/bisoxazolinephosphine-catalyzed asymmetric allylation of other hard nucleophiles in the future.[19]

ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures, characterization data, copies of ^{1}H, ^{13}C NMR spectra, HPLC spectra and X-ray crystal structures of compound **5** and **L1**-CuI. 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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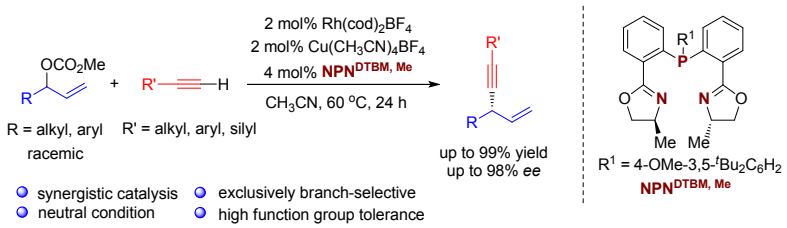
OCO2Me
R
+
R'—≡—H
2 mol% Rh(cod)2BF4
2 mol% Cu(CH3CN)4BF4
4 mol% NPNDTBM, Me
CH3CN, 60 °C, 24 h
R = alkyl, aryl
racemic
R' = alkyl, aryl, silyl
R'
R
up to 99% yield
up to 98% ee
synergistic catalysis
neutral condition
exclusively branch-selective
high function group tolerance
R1
P
O
N
N
O
Me
Me
R1 = 4-OMe-3,5-tBu2C6H2
NPNDTBM, Me