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Controllable Mono-/Dialkenylation of Benzyl Thioethers through Rh-Catalyzed Aryl C–H Activation

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C–H bond functionalization is a direct, economical, and efficient way to construct complex molecules that has drawn considerable attention in the past few decades.[1] One powerful and widely used strategy to improve the efficiency and control the selectivity of C–H activation is to introduce a directing group on the substrates.[2] In general, a relatively stable metallocycle intermediate can be formed with directing groups, promoting both the C–H activation and the subsequent functionalization. The most widely used directing groups usually contain sp^2-hybridized heteroatoms, including carbonyl-containing groups[3–9] and N-/O-containing heterocycles,[10] among others.[11] Several removable and/or transformable mono-/bidentate directing groups[12,13] have recently been developed. Other directing groups have also been explored recently by forming anions under basic conditions, including carboxylic acids, electron-deficient amides,[14] hydroxyl groups,[15] and carbon anions.[16] In comparison, neutral sp^3-hybridized heteroatoms have been less thoroughly investigated as directing groups (amines, ethers, and thioethers).[17–19] Herein, we report an sp^3-hybridized-thioether-directed C–H alkenylation through Rh catalysis.[19]

Recently, great progress has been made in the field of C–H functionalization through Rh catalysis.[20] Rhodium catalysis complements Pd catalysis because it has good functional-group tolerance and high catalytic efficiency, and many elegant examples have been reported recently.[21–23] Because the directing-group strategy is also one of the most powerful ways to increase selectivity in C–H functionalization, the development of new and useful directing groups in Rh catalysis is necessary to expand the applications of Rh-catalyzed C–H transformations.

In fact, sulfur-containing groups are rarely used as directing groups,[11b,c,13c,19] despite the development of several sulfur-tethered directing groups.[24] The use of a thioether as a directing group poses an extra challenge because of their ability to poison many transition-metal catalysts. However, their use as a directing group also has several advantages: 1) sulfur is contained in many natural and useful molecules,[25] functional materials, organocatalysts and water-reduction catalysts;[26] 2) a thioether directing group can be easily removed under reductive conditions either stoichiometrically or catalytically;[27] and 3) the thioether can undergo many other transformations.[28,29] To the best of our knowledge, there is no report introducing the thioether as a directing group in rhodium catalysis, although elegant examples of Pd-catalyzed transformations have been reported.[19] Herein, we report a successful example of controllable alkenylation through thioether-directed C–H activation under Rh catalysis. Most importantly, the selectivity between mono- and difunctionalization was well controlled by use of different solvents (Scheme 1a and b). Unactivated styrenes also react smoothly under the conditions provided (Scheme 1c). Sequential functionalization with two different alkenes was further achieved in a one-pot process (Scheme 1d). Furthermore, functionalized toluene derivatives can be obtained in one pot by direct treatment of the reaction mixture with Raney Ni (Scheme 1e).

Initially, we selected benzyl(methyl)sulfane (**1a**) and ethyl acrylate (**2a**) as model substrates to screen the reaction conditions (Table 1). Catalyst screening showed that Rh^{III} catalysts promoted the desired transformation and gave a mixture of the mono- and dialkenylation products (**3a** and **4a**, respectively) in the presence of $Cu(OAc)_2$ and AgOAc in methanol (Table 1, entries 1 and 2). Clearly, cationic catalyst $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ gave a better yield than $[\{RhCp^*Cl_2\}_2]$, with monoalkenylated **3a** as the major product (Table 1, entry 2). To our surprise, some other alcoholic solvents, for example, *t*BuOH and *tert*-AmylOH, inversed the selectivity and dialkenylated **4a** became the major product (Table 1, entries 8 and 9). This observation suggested the potential to control the selectivity of this alkenylation by changing the solvent.

First of all, we conducted the reaction of several representative substrates in different solvents to investigate the solvent effect (Table 2). Apart from styrene, the reaction of other substrates gave moderate to good yield and good selectivity; MeOH favors monoalkenylation whereas *t*BuOH favors dialkenylation. For styrene, the reactivity was low and a low yield was obtained (Table 2, entries 5 and 6). In-

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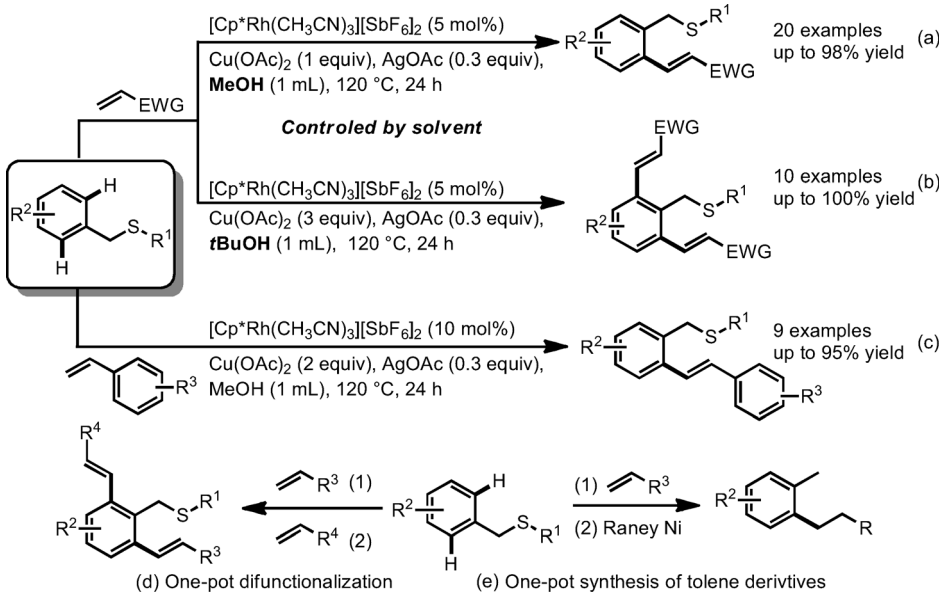
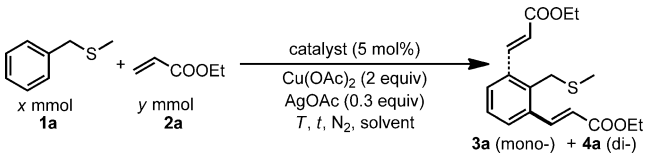


Scheme 1. Summary of this work (EWG = electron-withdrawing group; Cp* = pentamethylcyclopentadienyl).

Table 1. Catalyst screening and the solvent effect on the selectivity of mono- and dialkenylation.[a]



Entry	x	y	Catalyst (5 mol%)	Solvent	T [°C]	t [h]	Yield (mono/di) [%][b]
1	0.10	0.25	[{RhCp*Cl$_2$}$_2$]	MeOH	90	24	53.2:14.0
2	0.10	0.25	[Cp*Rh(CH$_3$CN)$_3$][SbF$_6$]$_2$	MeOH	90	24	79.7:28.3
3	0.10	0.25	[{Rh(cod)Cl}$_2$]	MeOH	90	24	trace
4	0.10	0.25	[Rh(CO)$_2$(acac)]	MeOH	90	24	trace
5	0.10	0.25	Pd(OAc)$_2$	MeOH	90	24	trace
6	0.10	0.25	[Cp*Rh(CH$_3$CN)$_3$][SbF$_6$]$_2$	EtOH	90	24	51.2:14.3
7	0.10	0.25	[Cp*Rh(CH$_3$CN)$_3$][SbF$_6$]$_2$	*i*PrOH	90	24	51.4:11.1
8	0.10	0.25	[Cp*Rh(CH$_3$CN)$_3$][SbF$_6$]$_2$	*t*BuOH	90	24	15.1:58.8
9	0.10	0.25	[Cp*Rh(CH$_3$CN)$_3$][SbF$_6$]$_2$	*tert*-AmylOH	90	24	17.8:79.5

[a] cod = 1,5-cyclooctadienyl; acac = acetylacetonate; *tert*-AmylOH = 2-methylbutan-2-ol [b] NMR spectroscopic yield with CH_2Br_2 the as internal standard.

creasing the reaction temperature and amount of styrene (**2d**) gave a better yield and selectivity (Table 1, entries 7 and 8). Although the ability of the solvent to control the selectivity was demonstrated by these substrates, the chemical yields were not good enough, so we conducted further optimization of the reaction conditions based on the results provided in Table 1 and Table 2.

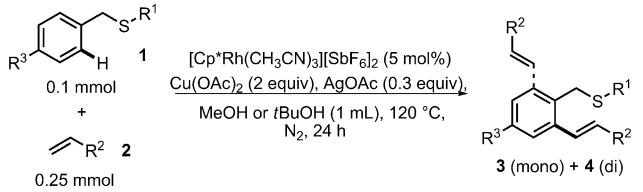
After systematic screening (Table S1 in the Supporting Information), we found that the best conditions (82%, Table S1, entry 13 in the Supporting Information) for forming monoalkenylated product **3a** were in the presence of $Cu(OAc)_2$ and AgOAc in MeOH when an excess of **1a** was present.[30] The key to selective dialkenylation was to change the solvent from methanol to *tert*-butanol (Table S2 in the Supporting Information). After the screening of conditions, a 93% yield of **4a** was obtained by increasing the amount of $Cu(OAc)_2$ (3.0 equiv) and **2a** (3.0 equiv), as well as slightly increasing the temperature (Table S2, entry 4 in the Supporting Information).

With the best conditions in hand, we explored the generality for the monoalkenylation (Table 3). With benzyl(methyl)sulfane (**1a**) as the model substrate, both methyl acrylate and butyl acrylate gave the corresponding products in high yields (**3b** and **3c**). As well as acrylates, acrylamides also underwent the alkenylation, albeit in lower yields (**3e** and **3f**). For methyl(naphthalen-2-ylmethyl)sulfane, the alkenylation occurred selectively in high yield at the β-position (**3d**) as a result of steric hindrance. Of other thioethers used in the reaction, the ethyl group showed excellent reactivity (**3g**). However, phenyl and tolyl groups gave low to moderate yields, respectively (**3h** and **3i**). The sensitivity of the reaction to the protecting group on sulfur probably resulted from slight changes in their electronic effects, which strongly affected the ability of sulfur to coordinate with the catalytic metal center. Other groups, mercapto, sulfinyl, sulphonyl, hydroxyl, and ether, all failed to result in reaction (**3j**, **3k**, **3l**, **3m**, **3n**).

Due to the facile preparation, benzyl(*para*-tolyl)sulfane derivatives were synthesized and used to investigate the functional group tolerance. Methyl substitution at *ortho*-, *meta*-, and *para*-positions all gave good to excellent results (**3n**, **3o**, and **3p**). Chloride, cyano, methoxyl, and ester groups were tolerated, giving acceptable yields (**3q**–**3u**). Comparably, electron-deficient substituents (**3r** and **3s**) are better than electron-rich groups (**3q** and **3t**), indicating that the C–H activation might occur through a concerted metalated dehydrogenation (CMD) rather than a direct electrophilic substitution pathway. Again, acrylamide showed slightly better reactivity than *N*,*N*-dimethylacrylamide (**3v** vs. **3w**). It is important to note that an internal alkene can also be used in the reaction, albeit in a lower yield (**3x**).

We further extended the scope of the reaction with respect to the alkene to include styrene derivatives (Table 4). To provide high efficiency, the amount of both catalyst and oxidant needed to be increased. (2-Methylbenzyl)(*para*-tolyl)sulfane (**1b**) was also used as the partner in this transformation and 2.5 equivalents of the styrene derivatives were

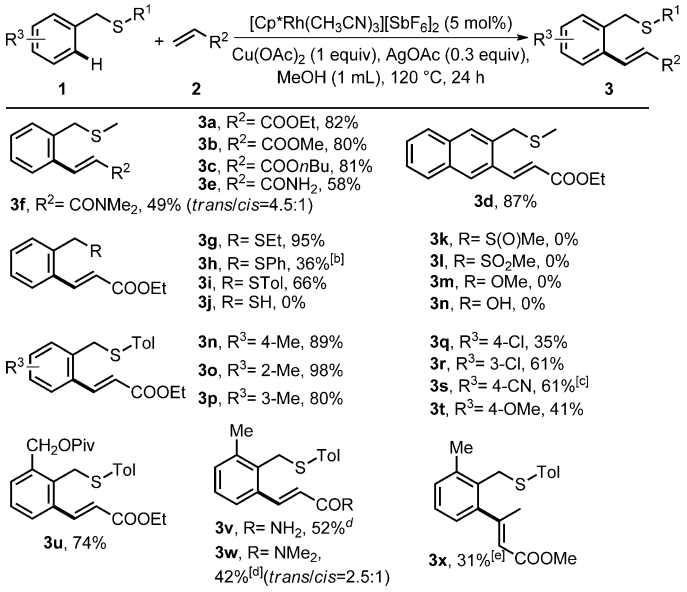
Table 2. Investigation of the solvent effect on the selectivity for mono- and disubstitution for several representative substrates.



Entry	**1** (R^1, R^3)	**2** (R^2)	Solvent	**3** [%][a]	**4** [%][a]	**3**/**4**
1	**1a** (Me, H)	**2a** (CO_2Et)	MeOH	79.7 (**3a**)	28.3 (**4a**)	2.8:1
2	**1a**	**2a**	*t*BuOH	15.1	58.8	1:3.9
3	**1a**	**2c** (CO_2Bu)	MeOH	82.9 (**3c**)	13.5 (**4c**)	5.5:1
4	**1a**	**2c**	*t*BuOH	13.5	90.6	1:6.7
5	**1a**	**2d** (Ph)	MeOH	36.8 (**3y**)	7.5 (**4y**)	4.9:1
6	**1a**	**2d**	*t*BuOH	46.2	23.6	2.0:1
7[b]	**1a**	**2d**	MeOH	48.7	13.4	3.6:1
8[b]	**1a**	**2d**	*t*BuOH	32.9	29	1.1:1
9	**1o** (Tol, H)	**2a**	MeOH	64.9 (**3i**)	9.8 (**4f**)	4.7:1
10	**1o**	**2a**	*t*BuOH	23.1	66.3	1:2.9
11	**1d** (Tol, Me)	**2a**	MeOH	59.5 (**3n**)	10.5 (**4h**)	5.7:1
12	**1d**	**2a**	*t*BuOH	38.5	70.1	1:1.9
13	**1i** (Tol, Cl)	**2a**	MeOH	40.3 (**3r**)	6.6 (**4g**)	6.1:1
14	**1i**	**2a**	*t*BuOH	42.3	58.6	1:1.4

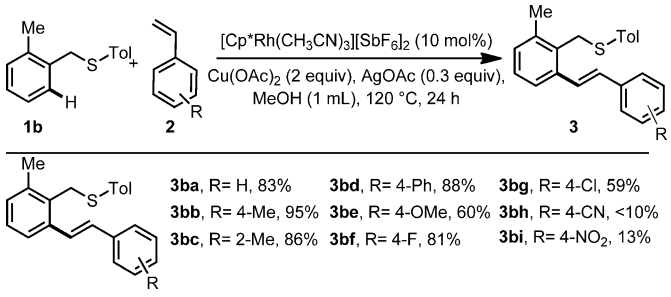
[a] NMR spectroscopic yield of the crude reaction system with CH_2Br_2 as the internal standard. [b] 3 equivalents of alkene were used at 120 °C.

Table 3. Monoalkenylation with various thioethers and electron-deficient alkenes.[a]



[a] Reaction conditions: Thioether (A, 0.2 mmol, 2 equiv), alkene (B, 0.1 mmol), catalyst $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ (5 mol%), oxidant $Cu(OAc)_2$ (1 equiv), and AgOAc (0.3 equiv), reacted in MeOH (1 mL) at 120 °C for 24 h under a N_2 atmosphere. [b] NMR spectroscopic yield with CH_2Br_2 as the internal standard. [c] 1 equivalent of A, 4 equivalents of B, 10% of Rh, and 4 equivalents of $Cu(OAc)_2$. [d] 1 equivalent of A, 3 equivalents of B, 10% of Rh, and 3 equivalents of $Cu(OAc)_2$. [e] 1 equivalent of A, 6 equivalents of B, 10% of Rh and 3 equivalents of $Cu(OAc)_2$, and *t*BuOH (1 mL) was used as the solvent.

Table 4. Substrate scope of styrene derivatives.[a]



[a] Reaction conditions: Thioether (**1b**, 0.1 mmol, 1 equiv), alkene (**2**, 0.25 mmol, 2.5 equiv), catalyst $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ (10 mol%), oxidant $Cu(OAc)_2$ (2 equiv), and AgOAc (0.3 equiv) reacted in MeOH (1 mL) at 120 °C for 24 h under a N_2 atmosphere.

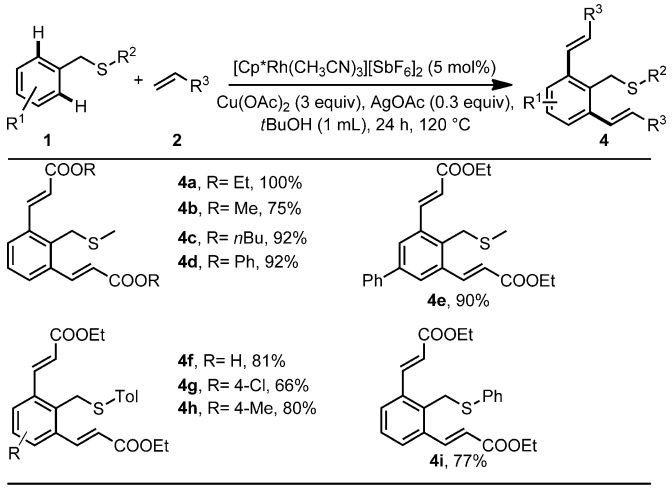
used. We found that styrene, 4-methylstyrene, and 4-vinyl-1,1′-biphenyl worked well and gave good to excellent yields (**3ba**, **3bb**, and **3bd**). Steric hindrance did not affect the reaction efficiency (**3bc**). Importantly, halogen atoms were tolerated, providing the possibility for orthogonal functionalizations[31] (**3bf** and **3bg**). Electron-rich and -deficient styrene derivatives both reacted smoothly to give the desired products, whereas electron-deficient alkenes were more reactive (**3be** and **3bf**). Unfortunately, nitro and cyano groups were not tolerated, probably as a result of the competitive coordination of the nitro and cyano groups to the metal center, thus inhibiting the C–H activation (**3bh**, **3bi**).

Subsequently, we investigated the substrate scope for the dialkenylation with the use of *tert*-butanol as the solvent (Table 5). We found that: 1) activated alkenes worked well and the desired products were obtained in excellent yields (**4a**, **4b**, **4c**, and **4d**); 2) different thioethers could be used as the directing groups with moderate to excellent reactivity (**4e**, **4f**, and **4i**); and 3) chloride survived well and the difunctionalized product was isolated in a moderate yield (**4g**).

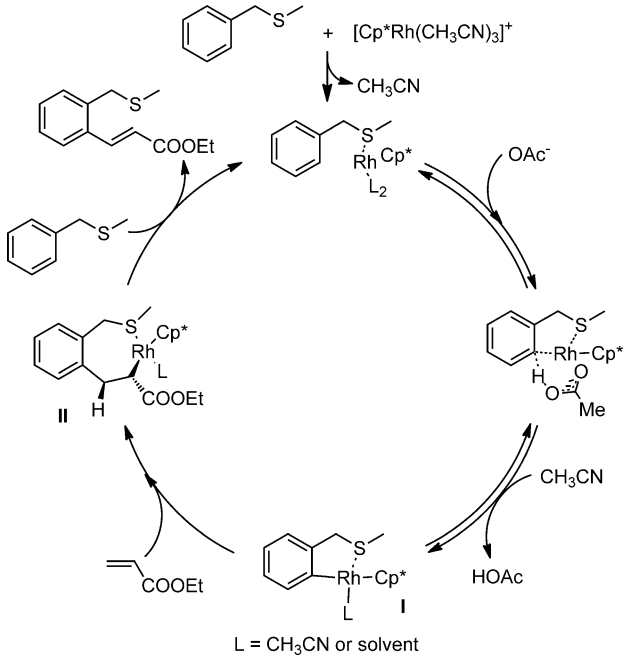
Since the mono- and dialkenylation have been carried out in different solvents, we set out to think about the stepwise alkenylation with different alkenes with the same catalytic system by changing the solvents in one pot. We removed methanol under vacuum from the product mixture of the first alkenylation and added a second alkene, more oxidant, and *t*BuOH as a solvent. To our delight, the sequential alkenylation of two different alkenes was achieved in 56% yield and high purity [Scheme 2, Eq. (1)]. Notably, if the catalyst was recharged, a quantitative yield was achieved in this sequential dialkenylation with different alkenes [Scheme 2, Eq. (2)].

In the deuterium-labeling experiments (Scheme 3), proton scrambling was observed, indicating that an equilibrium exists at the C–H activation step, which is inconsistent with previous reports about Rh^{III} catalysis.[23] Thus, we proposed the catalytic cycle shown in Scheme 4. With the assistance of

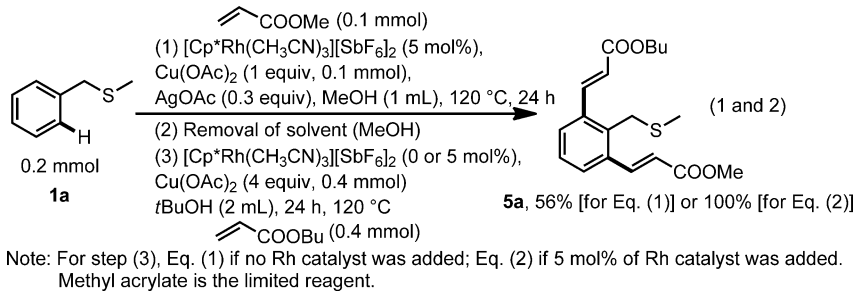
Table 5. Substrate scope of the dialkenylation.[a]



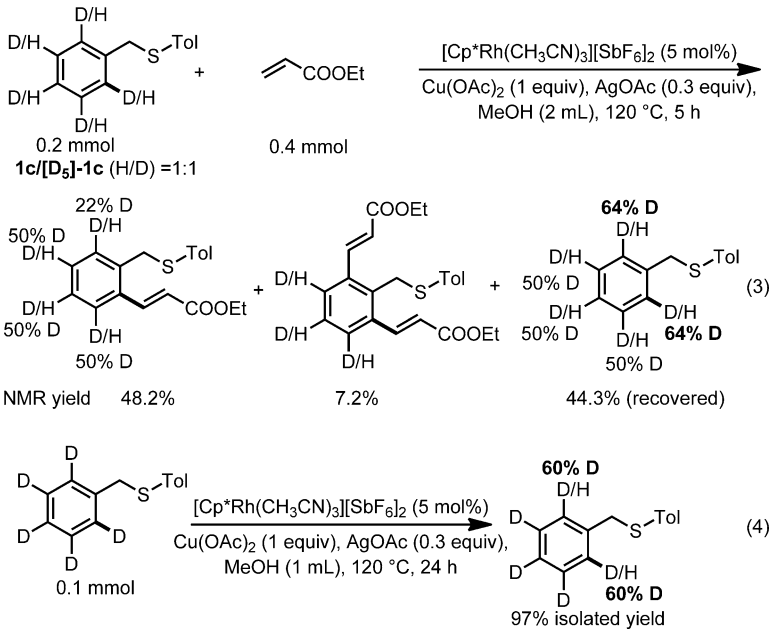
OAc^-, the sulfur-directed C–H activation proceeded through a CMD pathway to give 5-membered intermediate **I**. Subsequent alkene insertion and β-hydride elimination finished the catalytic cycle and released the final product.



Scheme 4. Proposed mechanism.



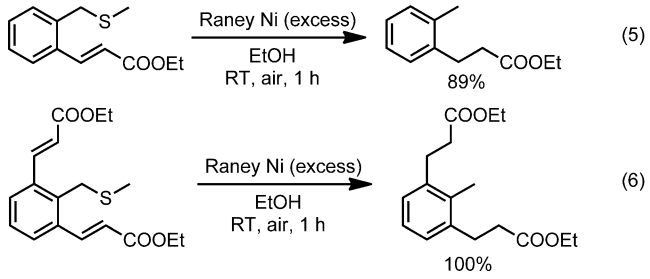
Scheme 2. Semi-one-pot dialkenylation reaction of thioether **1a** with two different alkenes.



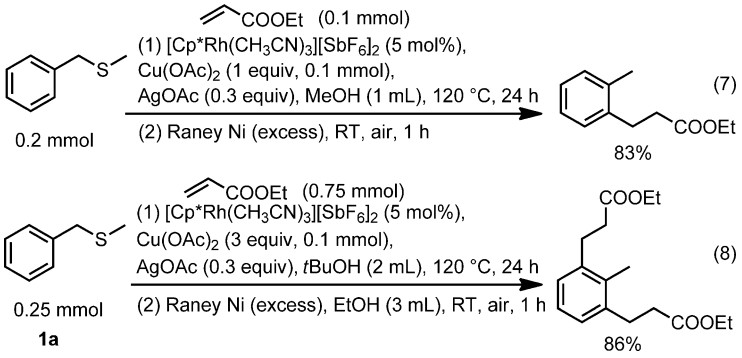
Scheme 3. Deuterium-labeling experiments (Tol = tolyl).

Further efforts have been made to explore the applications of this method. As we know, thioethers can easily be reduced under different conditions. For example, the alkenylated product has been submitted to the reduction conditions with Raney Ni in ethanol and the directing group can be easily removed at room temperature (Scheme 5). Notably, the alkenes were reduced at the same time, providing 3-phenylpropanoic acid derivatives (and toluene derivatives), which are important skeletons in organic synthesis [Eqs. (5) and (6)].[32] To simplify the procedure for these transformations, we constructed the alkylated toluene derivatives in a one-pot process by directly adding Raney Ni to the product mixture from the first alkenylation step [Scheme 6, Eqs. (7) and (8)]. This study provides a convenient process to make such useful chemicals.

In summary, we successfully developed the thioether-directed rhodium(III)-catalyzed sp^2 C–H alkenylation. In this



Scheme 5. Removal of the directing group.



Scheme 6. Semi-one-pot construction of toluene derivatives.

transformation, the substrate scope is quite broad and the yield is very high. By tuning the solvents, both mono- and difunctionalized products could be obtained selectively. With this method, sequential alkenylation with two different alkenes was achieved and well controlled. Further transformation of both the directing sulfide group and the olefin expanded the applications of this method. An investigation to understand the solvent effect involved in this transformation and explore its applications is underway.

Experimental Section

General procedure for monoalkenylation: Synthesis of 3 (Table 4): The catalyst $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ (4.2 mg, 0.005 mmol), copper acetate (18.6 mg, 0.1 mmol), and silver acetate (5.0 mg, 0.03 mmol) were added sequentially to a pre-dried Schlenk tube (50 mL) under an air atmosphere. The reaction tube was evacuated and filled with N_2. After addition of sulfide derivative **1** (0.2 mmol) and substituted alkene **2** (0.10 mmol) by microinjector, MeOH (1.0 mL) was injected, and then the reaction mixture was stirred in the sealed tube at 120 °C under a N_2 atmosphere in a Wattecs Parallel Reactor for 24 h. After cooling to RT, the product was purified by column chromatography on silica gel with petroleum ether/EtOAc (40:1 to 20:1) to afford compound **3** as a colorless liquid or oil.

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Keywords: alkenylation · C–H activation · rhodium · thioethers

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