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Rhodium-Catalyzed Asymmetric Allenylation of Sulfonylimines and Application to the Stereospecific Allylic Allenylation

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This work is dedicated to Professor Barry M. Trost in honour of his 75th birthday.

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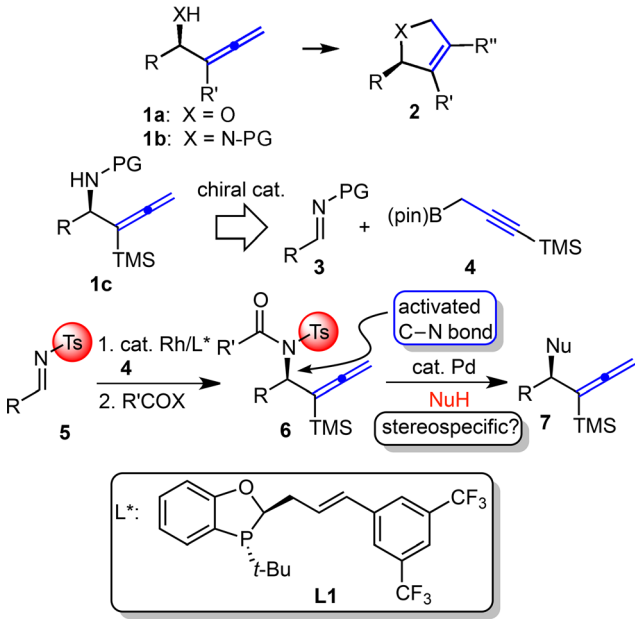
Abstract: The rhodium-catalyzed asymmetric allenylation of sulfonylimines is disclosed providing silyl homoallenylamide products in up to 99:1 *er*. Through subsequent activation of the C–N bond of the silyl homoallenyl sulfonamide, palladium-catalyzed stereospecific allylic allenylation could be achieved giving C–C bond formation with high chirality transfer. The synthetic utility of both the silyl homoallenyl sulfonamides and the silyl homoallenyl malonates as bis(nucleophiles) is demonstrated.

Keywords: allylic alkylation; asymmetric allenylation; palladium; phosphorus ligands; rhodium

The allene moiety is an extremely versatile functional group in organic synthesis. Over the years, the unique nature of this group containing both sp^2 and sp carbon atoms has been exploited for the preparation of valuable complex molecules in an efficient fashion by use of a broad array of different types of allene functionalization reactions enabled by a transition metal catalyst.[1] Many of these processes have employed the intramolecular cyclization of a heteroatom-based nucleophile on the allene group to form various important chiral heterocycles (Scheme 1, **1**→**2**).[1a,d,2] Therefore, methods to access enantioenriched chiral homoallenylamides **1b**/**c** represent a useful entry into these N-heterocycles in an asymmetric fashion. However, there are not many general, convenient, catalytic methods to prepare these materials in enantioenriched form. Of the asymmetric methods[3,4] available for the synthesis of enantioenriched homoallenylamides, Hoveyda's[4] recent reports demonstrate good generality employing borolane **4** as a nucleophile with protected imines [**3**, PG = P(O)Ph$_2$] facilitated by metal-boron exchange between the catalyst and **4**.

Recently, we have disclosed a new family of *P*-chiral *P*,π-hybrid ligands (Joshphos, **L1**) that are applicable in the asymmetric addition of arylboronic acids

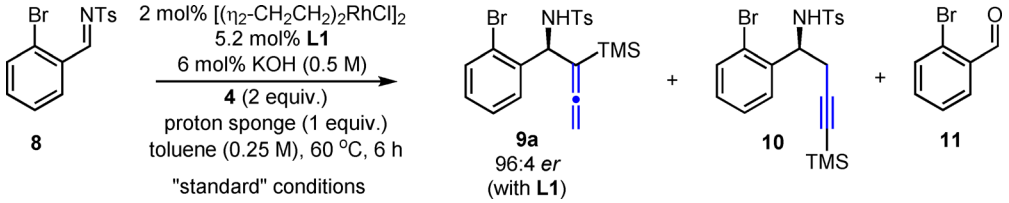


Scheme 1. Asymmetric allenylation and allylic allenylation.

to *N*-tosylaldimines enabled by Rh-boron exchange[5] between the boronic acid nucleophile and the Rh catalyst.[6] We reasoned that application of this catalytic system to Rh-boron exchange with **4** might enable an alternative asymmetric method to access **1c** (PG = Ts) from imine **5**. However, one complication is that borolane **4** can lead to propargylation or allenylation products[7] and, therefore, the catalyst must exquisitely control which mode of nucleophilic attack predominates. Additionally, due to the high electron-withdrawing nature of the *N*-tosyl group in the resultant allenylation products, we reasoned that C–N bond cleavage might be coaxed to occur by installation of an additional activating group (C=O, **6**) in conjunction with an appropriate catalyst such as Pd and, thereby, enable a stereospecific allylic allenylation to generate **7**. Somewhat surprisingly, stereospecific metal-catalyzed allylic allenylation has not been studied in general.[8] Therefore, this approach represents a new synthetic strategy to access other useful allenyl synthons (**7**) in an asymmetric fashion. Herein we disclose the development of the Rh-catalyzed asymmetric allenylation of *N*-tosylaldimines and demonstrate the ability of these products to be used in Pd-catalyzed stereospecific allylic allenylation with high chirality transfer.

We initially began by examining our Rh-JoshPhos catalytic system in the allenylation of imine **8**. Selected examples from this optimization study are given in Table 1. Gratifyingly, initial use of the conditions reported previously for the addition of arylboronic acids to imines[6] successfully gave the desired allene product with excellent enantioselectivity albeit with moderate yield (entry 1). The remaining mass balance in the reaction mixture was unreacted imine and significant amounts of aldehyde **11** formed from hydrolysis of **8**. Since the active Rh-OH catalyst is prepared *in situ* by use of aqueous KOH solution,[6] we began to explore the possibility of performing the process under "anhydrous" conditions to determine if imine hydrolysis could be circumvented. Replacement of the chiral catalyst by $[(cod)RhOH]_2$ in the absence of aqueous KOH gave poor conversion (entry 2); however, addition of water to this reaction improved conversion (entry 3). Additionally, the reaction was possible in the absence of KOH (entry 4). These results implied that a protic source was required for efficient catalyst turnover. Therefore, alcohol additives were tested. Replacement of H_2O with ROH under these conditions generally gave poor conversion except for when *i*-PrOH was employed (entry 5), but significant propargylation product **10** was obtained under these conditions. The reaction was then tested employing catalytic KOH prepared in ROH solvent (entries 6 and 7). In general, varying conversions and allene/propargyl selectivities were obtained, but it was noted that EtOH gave minimal amounts of aldehyde **11** (entry 6). Thus, the original reaction conditions employing aqueous KOH were re-examined using EtOH as additive (entry 8). Use of EtOH gave improved conversion without formation of propargylation product **10** and with minimal imine hydrolysis (entry 8). Increasing the reaction concentration in an effort to improve conversion led to increased amounts of propargylation product **10** over allenylation product **9a** (entries 9 and 10). Finally, use of EtOH in the ab-

Table 1. Rh-catalyzed allenylation of **8** employing borolane **4**.[a]



Entry	Variation from Standard Conditions	**9a**:**10**:**8**:**11**[b]
1	none	49:0:5:46
2	$[(cod)RhOH]_2$ used, no **L1** and KOH, 16 h	14:0:86:0
3	$[(cod)RhOH]_2$ and 3 equiv. H_2O used, no **L1** and KOH	50:0:5:46
4	no KOH, 6 equiv. H_2O added	29:0:25:46
5	no KOH, 1.2 equiv. *i*-PrOH added	35:53:12:0
6	KOH in EtOH instead of aqueous KOH	11:31:55:3
7	KOH in *i*-PrOH instead of aqueous KOH	21:6:26:47
8	1.1 equiv. EtOH added	72:0:22:6
9	1.1 equiv. EtOH added, [0.5 M]	19:30:9:42
10	1.1 equiv. EtOH added, [0.75 M]	0:64:9:27
11	no proton sponge, 1.1 equiv. EtOH added	34:0:66:0

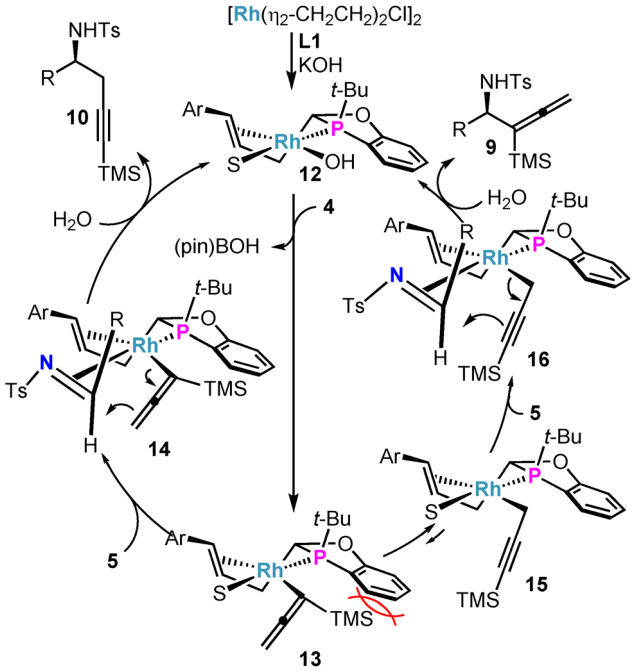
[a] Reactions performed using 0.09 mmol of **8**.
[b] Ratio determined by ^1H NMR spectroscopy of the unpurified reaction mixture. cod = 1,5-cyclooctadiene.

sence of proton sponge gave reduced conversion; however, no hydrolysis was observed under these conditions (entry 11). A survey of bases, reaction solvent, or variable amounts of EtOH did not lead to any additional improvements.

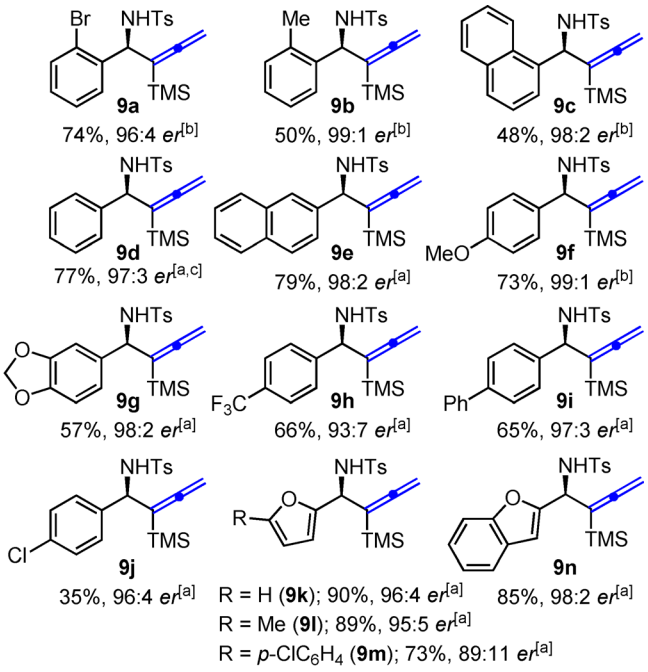
Based on our previous work employing arylboronic acids as nucleophiles with our (JoshPhos)RhOH catalyst (**12**, Scheme 2), a working mechanistic model for the proposed allenylation reaction is given in Scheme 2. Transmetalation of **4** with catalyst **12** could lead to either the allenyl complex **13** or propargyl complex **15**, however, literature precedents[4a,7g] and our observations on product distribution (**9a**/**10**) *vs.* reaction concentration (Table 1, entries 8–10) suggest that allenyl complex **13** forms initially. Due to steric demand between the TMS-group of the allene with the ligand backbone, Rh complex **15** is likely thermodynamically preferred and can be formed *via* a metallotropic rearrangement. Under standard condition concentrations (0.25 M), metallotropic rearrangement is faster than imine binding leading to **16** and ultimately affording exclusively the allenylation product **9** with the absolute stereochemistry predicted by the model of addition previously described.[6] However, at increased reaction concentrations (0.5–0.75 M), binding of imine can compete with isomerization of **13** to **15**, and therefore, increasing amounts of **10** are formed *via* **14**.

The scope of the Rh-catalyzed allenylation reaction (Scheme 3) was next tested using the best conditions identified for reaction optimization with imine **8** (Table 1, entries 8 and 11). For most imines examined, the optimal reaction conditions were in the absence of base at 80 °C (Conditions A). For substrates with *ortho*-substitution (**9a**–**9c**) or with a *para* electron-donating group (**9f**), addition of proton sponge gave improved yields (Conditions B). Both electron-rich and electron-deficient imines were tolerated in the reaction giving excellent enantioselectivities in all cases. Furanyl, substituted furanyl, and benzofuranyl imines were among the best substrates for the reaction (**9k**–**9n**).

With access to enantioenriched *N*-tosyl homoallenylamides **9**, we turned our attention to examining the proposed cleavage of the C–N bond to enable an allylic allenylation reaction (Scheme 1, **6**→**7**). In the context of allylic alkylation, Jung and co-workers[9] reported the use of either -N(Ts)$_2$ or -N(Ts)Piv as leaving groups in Pd-catalyzed allylic alkylation (Scheme 4, **17**→**18**). Surprisingly however, this type of leaving group[10] for allylic alkylation has been relatively under-utilized considering the intense research efforts by many groups in the field of catalytic allylic alkylation.[11] Therefore, to facilitate the ionization of the C–N bond in **9**, the acidic sulfonamide N–H needed to be blocked by an appropriate group. Additionally, for this approach to be practical, the yield for installation of the blocking group must be near quantitative. Based on Jung's precedent, we first tested the

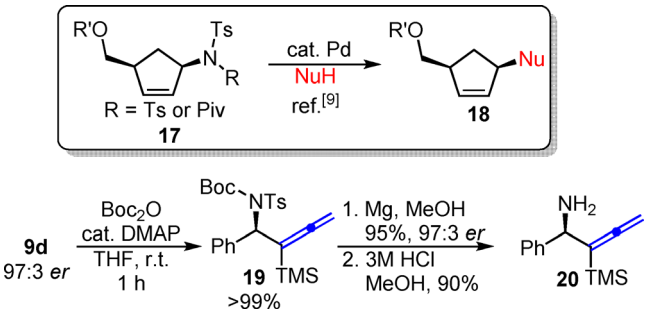


Scheme 2. Proposed catalytic cycle. S = solvent.



[a] *Reaction conditions A:* 0.2–0.6 mmol imine; Table 1, entry 11, 80 °C, 6 h.
[b] *Reaction conditions B:* 0.2–0.6 mmol imine; Table 1, entry 8.
[c] Reaction performed on a 1.0 g scale.

Scheme 3. Substrate scope for the addition of **4** to tosylimines.

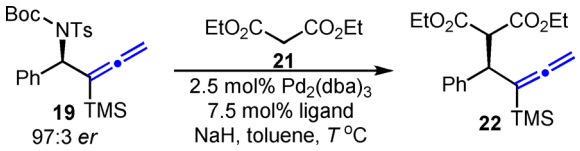


Scheme 4. Activation and deprotection of **9d**.

installation of an additional tosyl group or a pivaloyl group onto **9d**, but only poor yields of the desired products were obtained. We next chose to examine the use of a Boc group due to its inherent base stability and because it is well known that sulfonamides can be efficiently Boc-protected (Scheme 4).[12] Indeed, *N*-Boc sulfonamide **19** was easily prepared in quantitative yield. Furthermore, at this point, it was possible to cleave the tosyl group of **19** without racemization using Mg/MeOH,[13] and Boc-deprotection enabled the synthesis of **20** whose optical rotation was compared to the literature value[4a] to confirm the absolute configuration of **9d**. As already discussed, homoallenylamides have already been demonstrated by others to be extremely synthetically valuable, and thus, the deprotection methods described in Scheme 4 allow for the products formed through the Rh-catalyzed allenylation of *N*-tosylimines to also be applicable to these methodologies.[1a,d,2,4]

The stereospecific allylic allenylation employing *N*-Boc sulfonamide **19** was first examined using diethyl malonate as the nucleophile (Table 2). To obtain high chirality transfer in the alkylation process, trapping of the intermediate Pd complex after ionization of the homoallenyl leaving group by nucleophile must be significantly faster than π-σ-π isomerization that would lead to racemization. Therefore, we initially examined conditions that would be expected to be good for fast nucleophilic trapping (i.e., non-coordinating solvent, large ligand bite angle,[14] and high concentration; entries 1–4).[11e] Gratifyingly, the -N(Ts)Boc group was a suitable leaving group, and some erosion in enantiopurity was observed. While stereospecific Pd-catalyzed allylic allenylation has not been studied previously, the process is expected to be similar to Pd-catalyzed allylic alkylation.[11] In the context of Pd-catalyzed allylic alkylation, stereospecific alkylation from a chiral enantioenriched allylic leaving group has been widely studied[15] and is often referred to in the literature as the "chiral memory effect."[11e,16] It has been demonstrated for Pd-catalyzed allylic alkylation with terminal-unsubstituted chiral enantioenriched electrophiles that electron-rich phosphine ligands give improved chiral memory (i.e., chirality transfer).[15,17] However, in stark contrast to this precedent, use of electron-rich phosphines in the alkylation employing **19** gave almost complete racemization (entries 5 and 6).

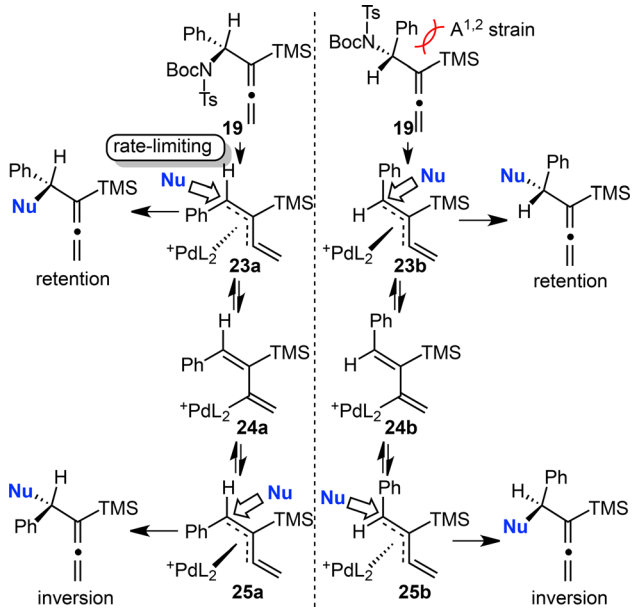
Table 2. Stereospecific allylic allenylation with malonate.[a]



Entry	Ligand (β_n)[b]	Temp.	Time	Yield [%]	*er*
1	dppb (94)	60 °C	1 h	91	87:13
2[c]	dppb (94)	60 °C	1 h	86	90:10
3	dppf (99)	60 °C	1 h	82	83:17
4	Xantphos (108)	60 °C	16 h	69	87:13
5[d]	PCy_3	80 °C	3 h	32	56:44
6[d]	P(*t*-Bu)$_3$	80 °C	3 h	82	50:50
7	(*R*)-BINAP (93)	75 °C	1 h	90	80:20
8	(*S*)-BINAP (93)	75 °C	6 h	92	96:4
9[e]	(*S*)-BINAP (93)	75 °C	4 h	69	54:46
10[e,f]	(*S*)-BINAP (93)	75 °C	5 h	88	50:50

[a] Reactions performed using 0.042 mmol of **19**; see the Supporting Information for details.
[b] Ligand bite angle from ref.[14]
[c] Reaction concentration doubled.
[d] 10 mol% ligand used.
[e] Racemic **19** was used.
[f] With 15 mol% $(n\text{-Bu})_4NCl$ and double the amount of solvent. dppb = 1,4-bis(diphenylphosphino)butane, dppf = 1.1′-bis(diphenylphosphino)ferrocene.

We next decided to test the effect of a readily available chiral ligand with a similar bite angle to that of dppb. Therefore, we chose to examine BINAP (entries 7–10). A matched/mis-matched effect was observed in terms of both reaction rate and chirality transfer: use of (*R*)-BINAP gave increased reaction rate but reduced chirality transfer, while (*S*)-BINAP gave reduced reaction rate but increased chirality transfer (entry 7 *vs.* 8). Because it could be argued that a chiral ligand could be employed to develop a dynamic kinetic asymmetric transformation (DYKAT) employing electrophile **19**, we tested the viability of a DYKAT process when employing *rac*-**19** (entries 9 and 10). Reaction with *rac*-**19** under identical conditions used with enantioenriched **19** gave rise to **22** with an enantiopurity of only 54:46 *er* (entry 9). This ratio would be expected based on the rates and selectivities observed when employing (*R*)- or (*S*)-BINAP individually with enantioenriched **19**. Of course, to obtain an efficient DYKAT, π-σ-π epimerization of the intermediate Pd complex is required for high selectivity.[11] Therefore, the experiment was repeated employing *rac*-**19** under conditions that would be expected to increase the rate of π-σ-π equilibration

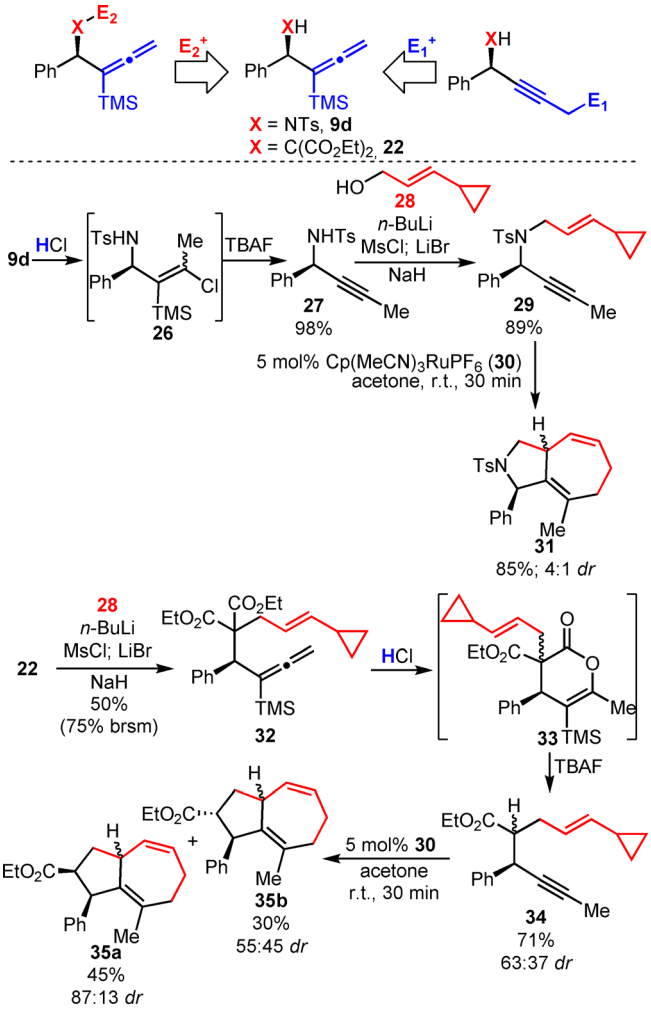


Scheme 5. Proposed mechanistic pathway for the allylic allenylation employing **19**.

(i.e., increased dilution with $(n\text{-Bu})_4Cl$ as additive; entry 10). In this case, racemic product was generated.

The results observed in the development of the stereospecific allylic allenylation in Table 2 can be rationalized by the mechanism given in Scheme 5. Ionization of the leaving group of **19** by Pd is expected to occur *via* the well-established[11] inversion mechanism leading to complexes **23**, respectively. Formation of **23a** is likely more favourable since generation of **23a** minimizes $A^{1,2}$-strain in **19** and leads to the alkene geometry of **23a** with the Ph and TMS groups in a *trans*-relationship. Fast nucleophile trapping of **23** must then occur for high chirality transfer to avoid racemization by equilibration of **23** through intermediate **24**. The results obtained using BINAP as the ligand imply that ionization of the leaving group of **19** is rate-limiting. Thus, (*R*)-BINAP gave faster overall reaction rate, but reduced enantiopurity because the Pd[(*R*)-BINAP] catalyst is presumed to have a matched ionization step but a mis-matched nucleophilic attack step in the catalytic cycle leading to erosion of enantiopurity. The converse would be true for the Pd[(*S*)-BINAP] catalyst rationalizing the improved enantiopurity, but reduced overall reaction rate.

The synthetic utility of the allene products is given in Scheme 6. Overall, these reagents can be viewed as orthogonal bis(nucleophiles). To demonstrate this, a simple proton was used for E_1^+. Treatment of **9d** with HCl gave clean hydrochlorination of the allene affording **26** that was then eliminated by treatment of the crude with TBAF to give alkyne **27**. Alkylation of **27** with the bromide of **28** led to enyne **29** that could be converted to the 5,7-bicycle.[18] Using the same



Scheme 6. Application of the allenylation products as orthogonal bis(nucleophiles) in complex molecule synthesis.

strategy, **22** was first alkylated at the malonate position to provide **32**. Treatment of **32** with HCl led to mainly trapping of the intermediate silyl-stabilized carbocation[19] by an internal ethyl ester group rather than by Cl^- resulting in dealkylation of one ester moiety to furnish lactone **33**. Treatment of crude **33** with TBAF led to silyl-elimination/lactone opening with concomitant decarboxylation generating **34**. The remaining mass balance was the alkyne still containing the diethyl malonate group (25%). Enyne cycloisomerization[18] of the diastereomeric mixture of **34** afforded **35** in good overall yield.

In summary, we have described a useful Rh-catalyzed asymmetric allenylation of *N*-tosylaldimines employing our *P*-chiral *P*,π-hybrid Joshphos-based ligands. In addition to these products being useful synthons due to the mild cleavage of the tosyl unit, application of these reagents to stereospecific allylic allenylation was demonstrated. This reactivity manifold that has not been studied previously with homoallenylamides allows for these reagents to also serve as pre-

cursors for the formation of enantioenriched C–C bonds.

Experimental Section

General Procedure A for the Rh-Catalyzed Allenylation of Sulfonylimines

To an 8-mL vial with magnetic stir-bar was sequentially charged ligand (5.2 mol%), chlorobis(ethylene)rhodium dimer (2.0 mol%), imine (1 equiv.), propargyl boronate (2 equiv.), and toluene (0.25 M) in a glove-box under an N_2 atmosphere. The mixture was allowed to stir for 10 min. Then, a freshly prepared and degassed 0.5 M solution of KOH in water (6.0 mol%) was added followed by ethanol (1.1 equiv.). The vial was capped, removed from the glove-box, and heated to 80 °C for 6 h. The mixture was cooled to room temperature, and 0.2 mL of 2 M HCl was charged, followed by 2 mL of water. The mixture was extracted with EtOAc (2×5 mL), and the combined organic layers were dried with Na_2SO_4 and concentrated under vacuum. The crude residue was then purified by flash chromatography on silica gel (Biotage, hexanes/EtOAc mixtures). Enantioselectivity was determined by chiral HPLC analysis.

General Procedure B for the Rh-Catalyzed Allenylation of Sulfonylimines

To an 8-mL vial with magnetic stir-bar was sequentially charged ligand (5.2 mol%), chlorobis(ethylene)rhodium dimer (2.0 mol%), imine (1 equiv.), propargyl boronate (2 equiv.), and toluene (0.25 M) in a glove-box under an N_2 atmosphere. The mixture was allowed to stir for 10 min. Then, a freshly prepared and degassed 0.5 M solution of KOH in water (6.0 mol%) was added followed by ethanol (1.1 equiv.) and stirred for 5 min. Proton sponge (1 equiv.) was then added. The vial was capped, removed from the glove-box, and heated to 60 °C for 6 h. The mixture was cooled to room temperature, and 0.2 mL of 2 M HCl was added, followed by 2 mL of water. The mixture was extracted with EtOAc (2×5 mL), and the combined organic layers were dried with Na_2SO_4 and concentrated under vacuum. The crude residue was then purified by flash chromatography on silica gel (Biotage, hexanes/EtOAc mixtures). Enantioselectivity was determined by chiral HPLC analysis.

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