Asymmetric Heck Reaction

Catalytic Desymmetrizing Intramolecular Heck Reaction: Evidence for an Unusual Hydroxy-Directed Migratory Insertion**

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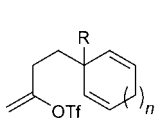
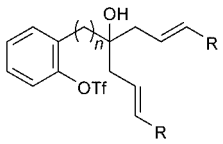
As reflected by a remarkable number of beautiful applications to the synthesis of structurally intriguing natural products,[1] the asymmetric intramolecular Heck reaction[2] has evolved as a prominent carbon–carbon bond-forming process.[3] The invention of asymmetric variants of Heck cyclizations has been approached by two distinct strategies: by indirect[4] and by direct[5] formation of stereogenic carbon centers.

Indirect construction of stereogenic carbons was realized by asymmetric Heck cyclization of prochiral precursors **A** (PG = protecting group), which emerged as privileged substrates for these so-called group-selective cyclizations. How-



A
(R = CO_2Me, CH_2OPG; n = 0, 1)



B
(R = H, aryl; n = 0, 1)

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ever, despite elegant investigations by Shibasaki et al.,[6] this methodology appears to be restricted to systems **A** in which the enantiotopic groups are incorporated into a cyclic framework.[7,8] Interestingly, desymmetrizing Heck cyclizations of less rigid systems **B** have not been reported so far.[9]

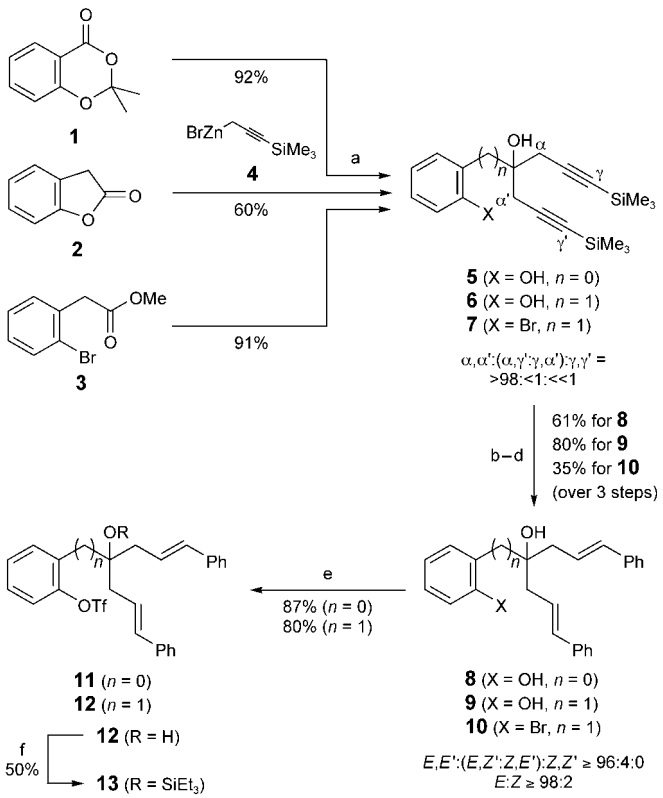
We envisioned compounds **B** as attractive substrates for an exploratory analysis of such desymmetrization reactions. In this paper, we wish to communicate the first catalytic desymmetrizing intramolecular Heck reaction of open-chain precursors **B** as well as experimental evidence for an unusual catalyst-directing hydroxy group[10] in these ring closures.

In the initial phase of the project, we extensively surveyed reaction conditions for the desymmetrization of prototype **B** (R = H, $n = 1$), but the enantiomeric excesses obtained were only moderate ($\leq 40\%$ *ee*).[11] These findings led us to consider the introduction of aryl groups at the terminal positions of the allyl moieties in **B** (R = Ph, $n = 1$). We anticipated that such a modification would have two beneficial effects: 1) prevention of post-Heck double-bond migration on account of the styrene unit and 2) improvement of enantioselectivity due to increased steric hindrance and aryl–aryl interactions.

The requisite cyclization precursors **11** and **12** were prepared starting from acetonide **1** and lactone **2**, respectively (Scheme 1). The direct synthesis of bishomoallylic alcohols from esters by twofold allylation employing γ-substituted allyl metal reagents is rather delicate since there is no general methodology available for controlling regio- and diastereoselectivity. We developed a reliable reaction sequence consisting of regioselective bispropargylation using zinc reagent **4** and diastereoselective reduction with aluminum hydrides.[12] Application of this procedure to **1** and enolizable **2** provided **5** ($n = 0$) and **6** ($n = 1$), respectively, in excellent regio- (**1**→**5** and **2**→**6**) and diastereoselectivities (**5**→**8** and **6**→**9**). Chemoselective triflation of final diol **8** was rather capricious due to the proximity of the hydroxy groups, whereas triflation of **9** proceeded smoothly (**8**→**11** and **9**→**12**, Scheme 1). The preparation of the corresponding aryl bromide **10** was accomplished by the identical protocol (**3**→**7**→**10**, Scheme 1).

When we subjected diene **12** to standard Heck reaction conditions (5.0 mol% $Pd(OAc)_2$, 7.5 mol% (*R*)-binap (**L1**), K_2CO_3, 80 °C) in various solvents,[13a] we were pleased to find exclusive formation of a single isomer **14**[14] with substantially improved enantioselectivity (Table 1, entry 1).[13b] Replacing **L1** by its cognate derivative **L2** resulted in slightly diminished selectivity (Table 1, entry 2); conversely, the novel binap surrogate (*S*)-Cl-MeO-biphep (**L3**),[15] for which applications in asymmetric Heck chemistry are unprecedented,[16] gave the best enantioselectivity (Table 1, entry 3).[17]

Complete conversion accompanied by enhanced enantioselectivity was achieved even at 60 °C and 50 °C (Table 1, entries 4–6). Though, intramolecular migration of the triflyl group (transtriflation) became a competing reaction pathway at temperatures below 50 °C and the prolonged reaction times required. In an attempt to prevent this undesired side reaction, we prepared the silyl ether of **12** (**12**→**13**, Scheme 1). Unexpectedly, cyclization of **13** under reaction conditions identical to those for **12** provided **15** in almost racemic form (Table 1, entry 7). Similarly, the deoxygenated substrate **17** furnished **18** with poor enantioselectivity (Scheme 2).[18]

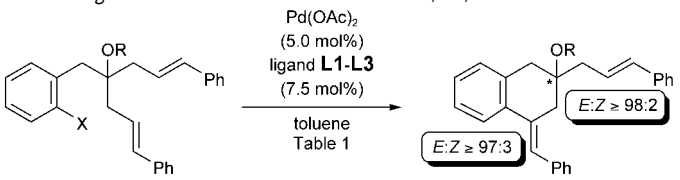


Scheme 1. Preparation of cyclization precursors **10**–**13**. Reaction conditions: a) **4**, THF, RT; b) TBAF·3 H_2O, THF, RT; c) PhI, $[Pd(PPh_3)_2Cl_2]$, CuI, Et_3N; d) Red-Al ($n = 0$) or $LiAlH_4$ ($n = 1$), THF, RT; e) Tf_2O, 2,6-lutidine, DMAP, CH_2Cl_2, −30 °C→RT ($n = 0$) and $PhNTf_2$, Cs_2CO_3, DMF, RT ($n = 1$); f) Et_3SiOTf, 2,6-lutidine, CH_2Cl_2, 0 °C. DMAP = 4-*N*,*N*-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, Red-Al = sodium bis(2-methoxyethoxy)aluminum dihydride, TBAF = tetra-*n*-butylammonium fluoride, Tf = trifluoromethanesulfonyl.

This pronounced effect (88 vs. 0–18% *ee*) indicated that the unprotected hydroxy group plays the pivotal role in the stereochemistry-determining step of the ring closure of **12**. A plausible assumption is that the free hydroxy group acts as a catalyst-directing group. We verified this further by conducting Heck cyclizations of **12** in the presence of equimolar amounts of an alcohol additive (MeOH or *t*BuOH).[19] Consistently, cyclization of **12** furnished **14** in merely moderate enantiomeric excess (Table 1, entries 8 and 9). Obviously, the external hydroxy group interferes with intramolecular coordination of the catalyst by the tertiary hydroxy group of **12**.

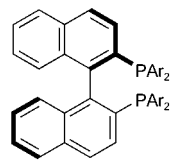
Moreover, ring closures of **17** and **12** occur at markedly different rates. Whereas the cyclization of **12** is complete after 20 h at 50 °C, conversion of **17** is low. This accelerating effect also supports the hypothesis that these Heck cyclizations involve intramolecular coordination of the catalyst.[20] Changing the position of the unprotected hydroxy group relative to the aryl triflate moiety had a similar effect. Bishomoallylic alcohol **11**, which produces a five-membered carbocycle, cyclized in low yield and poor enantioselectivity (**11**→**19**, Scheme 3).

Table 1: Desymmetrizing intramolecular Heck reactions of **10**, **12**, and **13**.[a]

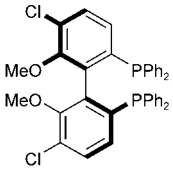


10 (X = Br, R = H)
12 (X = OTf, R = H)
13 (X = OTf, R = $SiEt_3$)

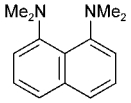
14 (R = H)
15 (R = $SiEt_3$)



L1 (Ar = Ph): (*R*)-binap
L2 (Ar = Tol): (*R*)-Tol-binap



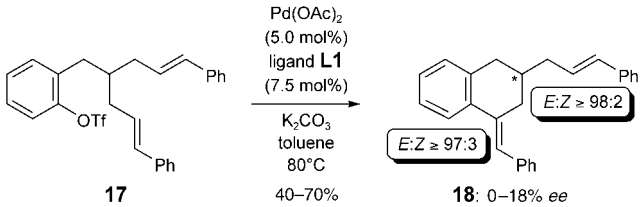
L3: (*S*)-Cl-MeO-biphep



16
proton sponge

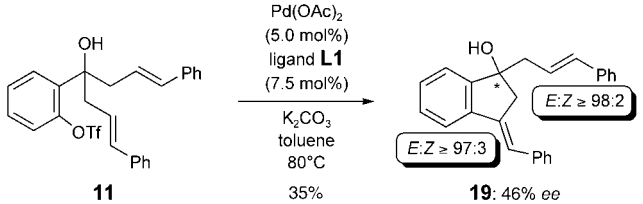
Entry	Precursor	Base, Additive	L	*T* [°C]	*t* [h]	Prod.	*ee* [%][b]	Yield [%][c]
1	**12**	K_2CO_3	**L1**	80	15	**14**	88	74
2	**12**	K_2CO_3	**L2**	80	15	**14**	80	81
3	**12**	K_2CO_3	**L3**	80	15	**14**	90[d]	81
4	**12**	K_2CO_3	**L1**	60	20	**14**	92	85
5	**12**	K_2CO_3	**L3**	60	20	**14**	94[d]	85
6	**12**	K_2CO_3	**L1**	50	20	**14**	92	85
7	**13**	K_2CO_3	**L1**	80	15	**15**	2[e]	55
8	**12**	K_2CO_3, MeOH[f]	**L1**	80	15	**14**	42	85
9	**12**	K_2CO_3, *t*BuOH[f]	**L1**	80	15	**14**	54	85[g]
10	**12**	TMP	**L1**	80	15	**14**	78	65
11	**12**	NaOAc	**L1**	80	15	**14**	86	85
12	**12**	**16**	**L1**	80	15	**14**	90	54
13	**12**	Cs_2CO_3	**L1**	80	15	**14**	–	–[h]
14	**10**	K_2CO_3	**L1**	80	15	**14**	12[d]	25[i]

[a] All reactions were conducted with a substrate concentration of 0.1 M in toluene with 4.0 equiv of the respective base. [b] Enantiomeric excess of the depicted *E*,*E*-configured diastereomer were measured by HPLC using a Daicel Chiralcel AD column (*n*-heptane:*i*PrOH = 90:10 at 15 °C). [c] Yield of analytically pure product isolated by flash chromatography on silica gel. [d] Absolute configuration opposite to that obtained for the cyclization of **12** using **L1** (Table 1, entry 1). [e] Enantiomeric excess was measured by HPLC using a Daicel Chiralcel AD column (*n*-heptane:*i*PrOH = 100:1 at 20 °C). [f] 1.0 equiv of anhydrous and degassed alcohol. [g] Approximately 80% conversion. [h] No product detected. [i] Reaction performed under conditions identical to those for **12**; yield not optimized. TMP = 2,2,6,6-tetramethylpiperidine.



17 40–70% **18**: 0–18% *ee*

Scheme 2. Desymmetrizing intramolecular Heck reaction of **17**.



11 35% **19**: 46% *ee*

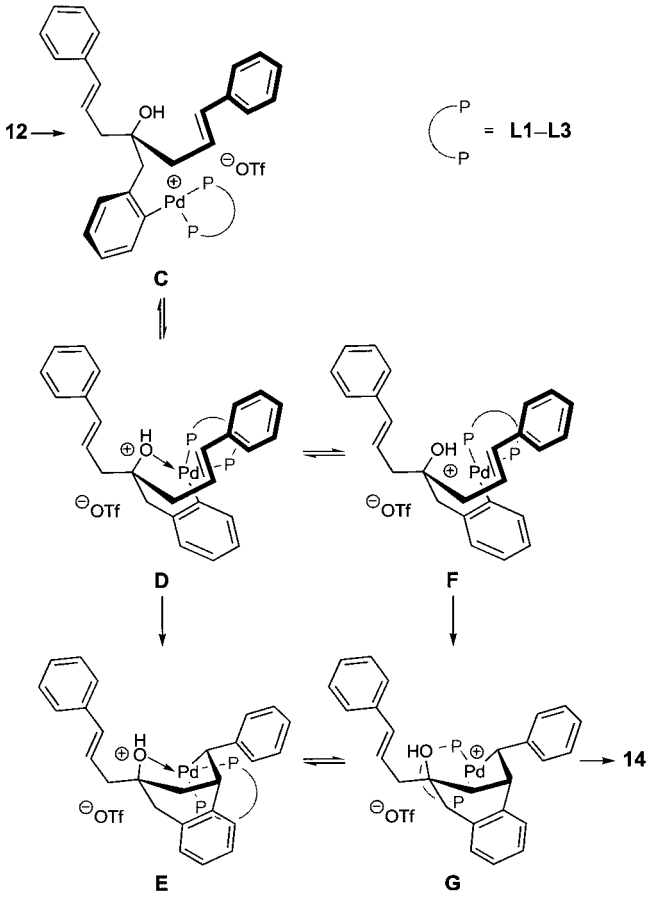
Scheme 3. Desymmetrizing intramolecular Heck reaction of **11**.

To clarify whether the free hydroxy or the corresponding alkoxy group functions as the directing group we screened several bases (Table 1, entries 10–13). Except for strong inorganic bases, all other bases tested had only minor influence on the enantiomeric purity of **14**. In particular, the enantioselectivity is unaffected when NaOAc is added, which implies that the free hydroxy group is possibly operating as a weak ligand for the palladium catalyst.

Coordination of the hydroxy group requires a free coordination site at the palladium center which, in principle, is available under so-called cationic reaction conditions.[2,3] In a control experiment, we performed the Heck cyclization under neutral conditions[21] employing the appropriate aryl bromide **10**. As expected, the level of enantioselectivity was low (Table 1, entry 14). Based on these observations, we propose a mechanism in which the cationic arylpalladium species **C** is reversibly coordinated by the tertiary hydroxy group to form a six-membered ring (**C** and **D**, Scheme 4). The fate of key intermediate **D** is unclear since migratory alkene insertion involving pentacoordinate palladium complexes is not completely understood (**D**→**E**).[21,22]

In our case, a modified scenario appears to be likely: coordination of the hydroxy group in **D** generates a highly ordered transition state which allows for efficient differentiation of the formerly enantiotopic branches. Either a dissociative (**D**→**F**→**G**) or an associative (**D**→**E**→**G**) migratory insertion is a plausible reaction pathway providing **14**. The high enantioselectivity observed for **12** could stem from the ideal proximity of the hydroxy group and the palladium center.[23]

In summary, we have elaborated a catalytic desymmetrizing intramolecular Heck reaction of a structurally novel substrate class. These investigations have revealed a conceptually interesting role of a hydroxy group as a catalyst-directing group in an asymmetric Heck reaction.[10] In addition to further studies directed towards a more refined mechanistic understanding, we are currently exploring the use of chiral alcohols as additional ligands in asymmetric Heck reactions. Application of this methodology to the formal total synthesis of anthracyclines will be reported in due course.[24]



Scheme 4. Catalyst-directing hydroxy group.

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Keywords: asymmetric catalysis · asymmetric synthesis · C–C coupling · palladium

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