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Asymmetric Synthesis of α-Substituted Aldehydes by Pd-Catalyzed Asymmetric Allylic Alkylation–Alkene Isomerization–Claisen Rearrangement

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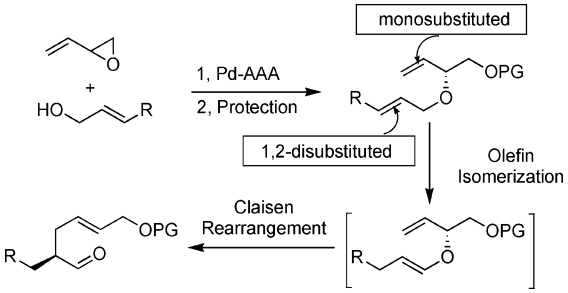
ABSTRACT



Enantiospecific aliphatic Claisen rearrangement was realized with generally high chirality transfer. The requisite substrates were synthesized via Pd-catalyzed asymmetric allylic alkylation (AAA) from easily obtained starting materials. After protection, the resultant bisallyl ethers underwent olefin isomerization and in situ Claisen rearrangement (ICR) to generate α-chiral aldehydes. Remarkable chemoselectivity in the olefin isomerization step was observed. An asymmetric synthesis of communiol A was accomplished applying this methodology.

The aliphatic Claisen rearrangement constitutes an important synthetic method with much more potential than has yet been realized.[1] On the other hand, the Ireland ester enolate Claisen rearrangement has had much more use which may be attributed to (1) the ease of access of the requisite substrates and (2) the development of asymmetric versions.[2] Our development of an asymmetric synthesis of bisallyl ethers via Pd asymmetric allylic alkylation (AAA) led us to question whether such intermediates could undergo chemoselective isomerization to allyl vinyl ethers which would undergo the Claisen rearrangement in situ, a process termed isomerization−Claisen rearrangement (ICR) by Nelson.[3−5] Herein, we report our studies in this transformation sequence. We wish to report the realization of this sequence with a most surprising chemoselectivity.

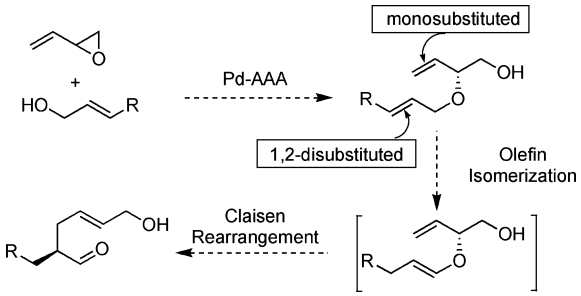


Figure 1. Planned vinyl epoxide opening and isomerization−Claisen rearrangement sequence.

As shown in Figure 1, the less-substituted olefin in the resulting bisallyl ether was expected to isomerize given the

(1) (a) Ziegler, F. *Chem. Rev.* **1988**, *88*, 1423. (b) Hiersemann, M.; Abraham, L. *Eur. J. Org. Chem.* **2002**, 1461. (c) Nubbemeyer, U. *Synthesis* **2003**, 961. (d) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939.

(2) (a) Ito, H.; Taguchi, T. *Chem. Soc. Rev.* **1999**, *28*, 43. (b) Chai, Y.; Hong, S.; Lindsay, H. A.; McFarland, C.; McIntosh, M. C. *Tetrahedron* **2002**, *58*, 2905.

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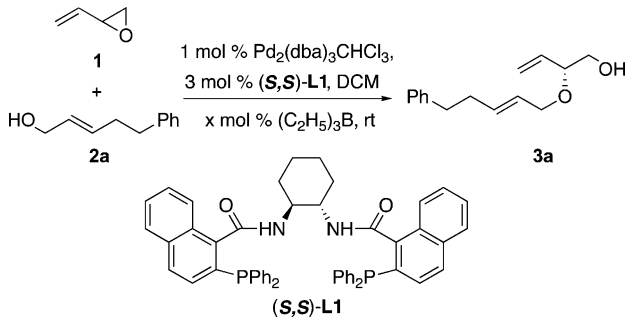
thermostability and steric hindrance of the multisubstituted olefin. However, in our substrate system, the remarkable reverse phenomenon was observed: the isomerization took place on the 1,2-disubstituted olefin instead of on the monosubstituted olefin. Furthermore, the issue of chirality transfer in the Claisen rearrangement arises. When there is only one stereogenic center existing both before and after the Claisen rearrangement, complete chirality transfer should be more difficult because of lower conformational rigidity in the Claisen transition state.

The initial trial for the AAA of butadiene monoepoxide with 1 mol % of $(C_2H_5)_3B$ resulted in 29% yield and 82% enantiomeric excess with the reaction finishing within 1 h (Scheme 1).[5] We postulated that the low yield resulted from

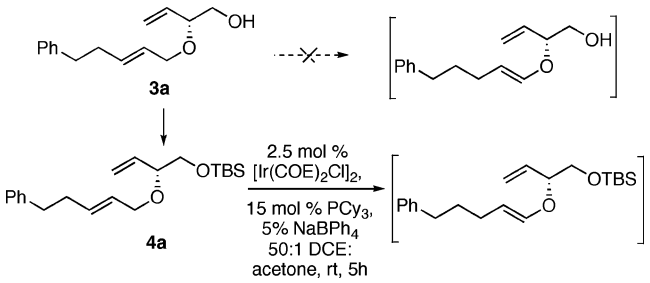
Scheme 1. Pd-AAA



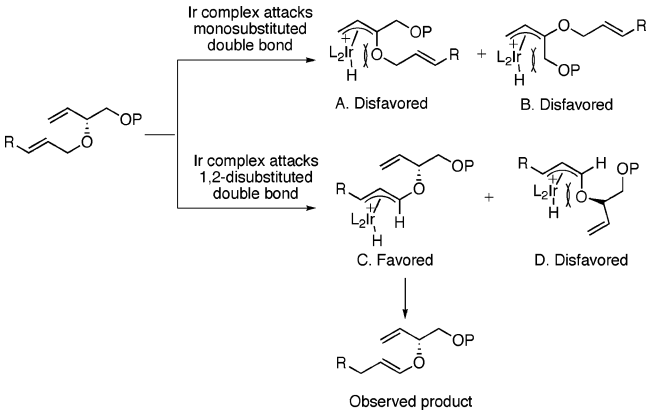
the competition of the product alcohol for the palladium reaction to produce oligomeric species. Slow addition of vinyl epoxide only slightly improved the yield to 41%. Increasing the temperature did not improve the yield or the ee, whereas lowering the temperature to 0 °C decreased the ee to 37%. With an excess amount of allylic alcohol, the yield increased to 74%, as the excess alcohol both increased the conversion of vinyl epoxide and suppressed the oligomer formation. Fortunately, the excess amount of allylic alcohol was recovered almost quantitatively after the reaction. The borane cocatalyst was observed to have the greatest impact on the enantioselectivity. A higher borane loading to 5% decreased the ee to 68%, whereas lowering the loading to 0.5% or 0.2% gave 87−89% or 90% ee, respectively. The sterically more hindered borane, tri-*sec*-butylborane, gave a 2% increase in ee but resulted in 32% lower yield and required a much longer reaction time than with $(C_2H_5)_3B$.

Screening conditions for isomerizing the bisallyl ether **3a** showed that, although the conversions were extremely low in most cases, iridium catalysts gave the best *E* selectivity.[6] Different hydride sources including H_2 gas, $NaBH_4$, triethylsilane, and formic acid were also examined yet without encouraging results. The highest conversion (10%) was

Scheme 2. Olefin Isomerization

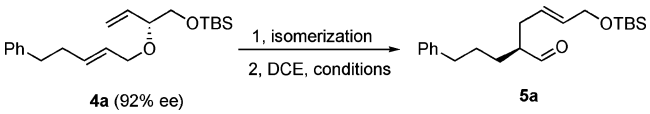


Scheme 3. Chemoselectivity of the Double-Bond Isomerization



achieved by using 5 mol % of $[Ir(COD)(PPh_3)_2]PF_6$ in combination with H_2 gas in methylene chloride at room temperature.[6a] Utilizing conditions reported by Nelson and co-workers gave only trace conversion after 5 h.[4] Therefore, we postulated that the hydroxyl group on the bisallyl ether

Table 1. Optimization for Chirality Transfer of the Claisen Rearrangement[a]



entry	condition of rearrangement	product % ee
1	heat, 80 °C, 59 h	72
2	microwave, 150 °C, 10 min	83
3	microwave, 140 °C, 15 min	85
4	microwave, 130 °C, 20 min	83
5	1 equiv of BSA, microwave, 140 °C, 15 min	88
6	add 2 equiv of MAD[b], DCM, −78 °C, 1 h	no reaction
7	add 2 equiv of MAD[b], DCM, rt, 1 h	no reaction

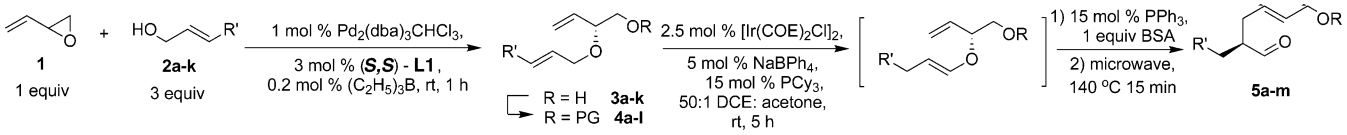
[a] The yields of the reactions were 70−80%. [b] MAD = methyl aluminum bis(2,6-di-*tert*-butyl-4-methylphenolate).

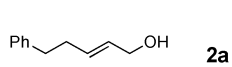
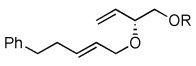
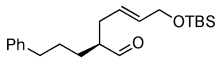
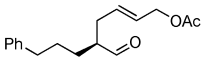
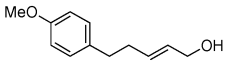
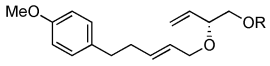
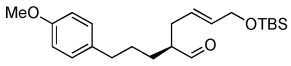
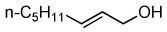
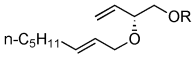
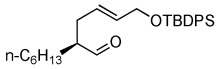
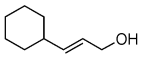
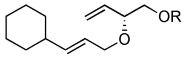
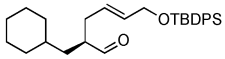
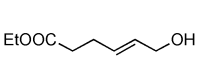
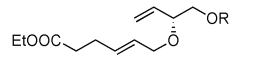
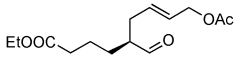
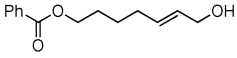
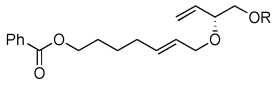
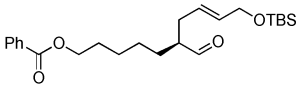
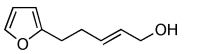
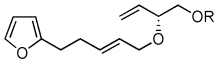
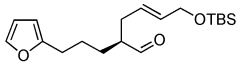
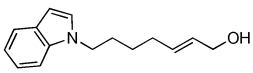
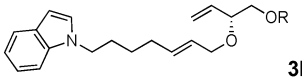
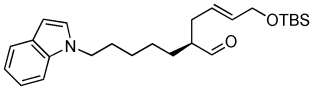
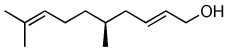
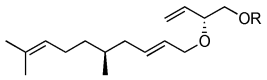
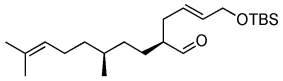
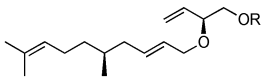
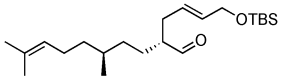
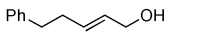
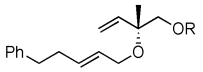
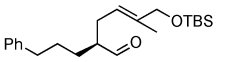
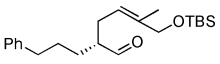
(3) For early development of ICR, see: (a) Reuter, J. M.; Salomon, R. G. *J. Org. Chem.* **1977**, *42*, 3360. (b) Swenton, J. S.; Bradin, D.; Gates, B. D. *J. Org. Chem.* **1991**, *56*, 6156.

(4) Recent development of ICR: (a) Nelson, S. G.; Bugard, C. J.; Wang, K. *J. Am. Chem. Soc.* **2003**, *125*, 13000. (b) During the final stage of our study, an asymmetric version generating vicinal stereogenic centers was reported. See: Nelson, S. G.; Wang, K. *J. Am. Chem. Soc.* **2006**, *128*, 4232.

(5) Pd-AAA of vinyl epoxide with alcohol nucleophiles: Trost, B. M.; McEachern, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 12702.

Table 2. Optimized Conditions and Reaction Scope

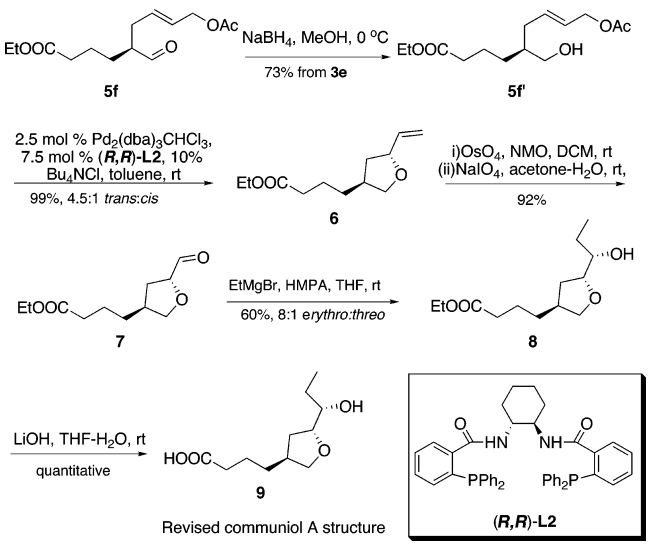


entry	allylic alcohol	diallyl ether[a] R=H % yield (% ee)[b]	R=PG[c] % yield	Claisen product % yield[d] (% ee)[e]	% ct[f]
1	 **2a**	 **3a** 74(90)	TBS **4a** 86	 **5a** 72(86)	96
2			Ac **4b** 94	 **5b** 72(86)	96
3	 **2b**	 **3b** 85(91)	TBS **4c** 97	 **5c** 70(87)	96
4	 **2c**	 **3c** 76(90.6)	TBDPS **4d** 96	 **5d** 70(90)	99
5	 **2d**	 **3d** 80(88)	TBDPS **4e** 97	 **5e** 61(86)	98
6	 **2e**	 **3e** 77(90)	Ac **4f** 97	 **5f** 73(86)	96
7	 **2f**	 **3f** 78(90)	TBS **4g** 90	 **5g** 82(79)	88
8	 **2g**	 **3g** 70(90)	TBS **4h** 93	 **5h** 72(88)	98
9	 **2h**	 **3h** 80(91.5)	TBS **4i** 82	 **5i** 70(87)	95
10	 **2k**[g]	 **3i** 67(91)[h]	TBS **4j** 96	 **5j** 74(90)[h]	99
11		 **3j**[i] 64(91)[h]	TBS **4k** 98	 **5k** 71(90)[h]	99
12	 **2a**	 **3k** 76(99)[j]	TBS **4l** 98	 **5l** 47[j](88)[k]	89
				 **5m** 20[j](88)[k]	89

[a] Yields were reported for the AAA step where R = H and for the protection step where R = PG (protecting group). [b] Determined by chiral HPLC for the alcohols or the corresponding silyl ether derivatives of the AAA products. [c] TBS = *tert*-butyldimethylsilyl; Ac = acyl; TBDPS = *tert*-butyldiphenylsilyl. [d] Yields were reported for the in situ reduction products **5a′**−**5m′** of the resulting aldehydes to prevent racemization during chromatography isolation (*E*/*Z* > 30:1, separable). [e] Determined by chiral HPLC for the alcohols or the corresponding benzoates of the in situ reduction products or by ^{1}H NMR for the corresponding *O*-methylmandelates. In the case of entry 6, the ee was determined by chiral HPLC for the *O*-methylmandelate derivative. [f] % ct (chirality transfer) = product's ee/substrate's ee. [g] 98% ee for **2k**. [h] Diastereomeric excesses rather than enantiomeric excesses were reported. [i] (*R*,*R*)-**L1** was used in the AAA step. [j] Isoprene monoepoxide was used instead of butadiene monoepoxide in the AAA step. [k] Two separable *Z*,*E* isomers were obtained after the Claisen rearrangement.

might have interfered with the catalytic cycle by saturating the open coordination site on the Ir catalyst. Indeed, after protecting the free OH with a *tert*-butyldimethylsilyl group, 25% conversion was achieved with 5 mol % of [Ir(COD)-$(PPh_3)_2$]PF_6/H_2 under the above conditions. More satisfyingly, by revisiting Nelson's conditions, full conversion of the protected diallyl ether was obtained by using 2.5 mol % of $[(C_8H_{14})_2IrCl]_2$, 15 mol % of PCy_3, and 5 mol % of $NaBPh_4$

Scheme 4. Synthesis of the Revised Structure of Communiol A



in 50:1 DCE/acetone at room temperature after 5 h (Scheme 2). Notably, the isomerization took place exclusively at the 1,2-disubstituted double bond with high *E* selectivity (the *Z* isomer was undetectable by ^{1}H NMR). A possible rationale depicted in Scheme 3 takes into consideration the allylic strain in a 1,1-disubstituted allyl complex compared to a 1,3-disubstituted one.

The Claisen rearrangement would result in an α-chiral aldehyde, which tends to racemize. Thus, striking a balance between time and temperature for the rearrangement was crucial for the chirality transfer. Simple heating of the reaction proved to be inefficient for our substrate both in conversion and in selectivity (Table 1, entry 1). Therefore, a chemical microwave was applied and afforded full conversion at 150 °C within 10 min (Table 1, entry 2). Further optimization showed that using a microwave at 140 °C for 15 min gave the least chirality loss (Table 1, entry 3). Adding 1 equiv of *O*,*N*-bistrimethylsilylacetamide (BSA) could further inhibit the racemization (Table 1, entry 5). Lewis acid catalyzed Claisen rearrangement was also attempted but did not bring down the required temperature with acceptable conversion or chirality transfer (Table 1, entries 6 and 7). The optimized conditions and substrate scope for Pd-AAA−ICR are summarized in Table 2.[7]

(6) Selected olefin isomerization references: (a) Matsuda, I.; Kato, T.; Sato, S.; Izumi, Y. *Tetrahedron Lett.* **1986**, *27*, 5747. (b) Frauenrath, H.; Runsink, J. *J. Org. Chem.* **1987**, *52*, 2707. (c) Frauenrath, H.; Sawicki, M. *Tetrahedron Lett.* **1990**, *31*, 649. (d) Hu, Y.-J.; Dominique, R.; Das, S. K.; Roy, R. *Can. J. Chem.* **2000**, *78*, 838.

Realizing the protecting group's influence on the conversion and chirality transfer was close to none (Table 2, entries 1 and 2), we envisioned that the protecting group could actually be turned into a leaving group, leading to the synthesis of useful building blocks. A short synthesis of the revised structure of communiol A was completed as an example (Scheme 4). Starting from the known allylic achohol **2e**, the Pd-AAA−acylation−ICR sequence gave aldehyde **5f** (Table 2, entry 6), which was in situ reduced to the corresponding primary alcohol **5f′**.[8] A Pd-catalyzed ring-closure reaction developed by our group afforded the 2,4-disubstituted tetrahydrofuran in a 4.5:1 trans/cis ratio.[9] Following the oxidative cleavage of the terminal olefin, Grignard addition using an excess amount of 2:1 HMPA/EtMgBr resulted in product **8** with an 8:1 erythro/threo ratio of separable diastereomers.[10] Hydrolysis of ethyl ester furnished the revised communiol A structure **9**.[11]

In summary, we have reported a Pd-AAA−ICR sequence with generally high chirality transfers and an unusual chemoselectivity in the isomerization step. The reaction scope is relatively broad, and the products can form useful building blocks through simple transformations as exemplified by the synthesis of communiol A.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Absolute configuration: **3a**−**l** were established by analogy to our previous work (ref 5); **5a**−**m** (**5a′**−**m′**) were proposed by the chair transition states of Claisen rearrangement, among which **5a′**, **5l′**, and **5m′** were degraded to known γ-phenylpropylsuccinic acid, and the absoluted configurations were confirmed by comparing the optical rotation signs with (*D*)-(+)-γ-phenylpropylsuccinic acid. Trost, B. M.; Zhang, T. unpublished results.

(8) Casara, P. *Tetrahedron Lett.* **1994**, *35*, 3049.

(9) Trost, B. M.; Machacek, M. R.; Faulk, B. D. *J. Am. Chem. Soc.* **2006**, *128*, 6745.

(10) (a) Amouroux, R.; Ejjiyar, S.; Chastrette, M. *Tetrahedron Lett.* **1986**, *27*, 1035. (b) Jefford, C. W.; Jaggi, D.; Boukouvalas, J. *Tetrahedron Lett.* **1986**, *27*, 4011.

(11) Isolation and synthetic studies of communiols: (a) Che, Y.; Gloer, J. B.; Scott, J. A.; Malloch, D. *Tetrahedron Lett.* **2004**, *45*, 6891. (b) Kuvahara, S.; Enomoto, M. *Tetrahedron Lett.* **2005**, *46*, 6297. (c) Murga, J.; Falomir, E.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2005**, *46*, 8199.