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A Highly Stereoselective Sequential Allylic Transfer Reaction of Diene with Diboronyl Reagent and Aldehydes Promoted by Nickel Catalyst

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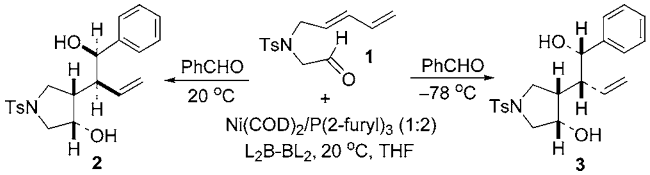
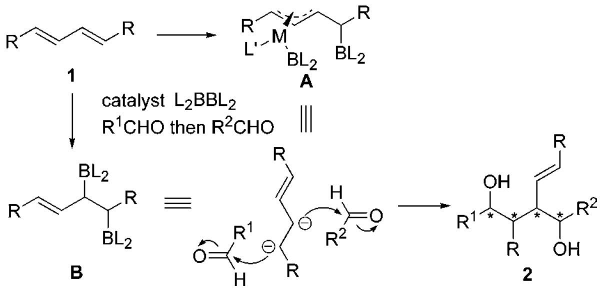
ABSTRACT



A new protocol for the sequential allylic transfer reaction of a diene with two aldehydes in the construction of cyclic systems containing four stereogenic centers is achieved in a one-pot operation. Reaction of the diene-alehyde 1 with aldehyde in the presence of the diboronyl reagent catalyzed by a nickel complex produces products 2 and 3 depending on reaction conditions in high levels of diastereoselectivity. Extension of this method to the synthesis of six-membered rings is also investigated.

The allylic transfer reactions of allylic metals to carbonyl groups provide excellent stereoselective routes to the corresponding alcohols.[1] Although there have been elegant reports regarding allylboration of carbonyl functionalities,[2] the scope of the reaction is still limited to establishing two stereogenic centers. In the course of our research program aimed at finding new synthetic methods in the stereoselective construction of pyran rings via sequential allylic transfer reactions,[3] we disclosed our discovery on the transition-metal-catalyzed intramolecular allylation between allene and carbonyl functionality to afford cyclic compounds in high levels of stereoselectivity.[4] During this research program, we became quite interested in designing a sequential allylic transfer reaction from a diene and diboronyl reagent with two aldehydes by a transition metal catalysis to form **2** with the generation of four contiguous stereogenic centers as depicted in Scheme 1.

Scheme 1



It was envisaged that the sequential allylic transfer reaction of **1** with two different carbonyl compounds leading to the formation of **2** could be realized through two reaction routes as described in Scheme 1. To provide direct access to product **2**, we considered the potent precursors **A** and **B**, which would

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(1) For general discussions for allyllations, see: (a) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763−2793. (b) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; pp 299−401. (c) Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; pp 403−490.

(2) For a review, see: Roush, W. R. In *Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Vol. 3, pp 1410−1486.

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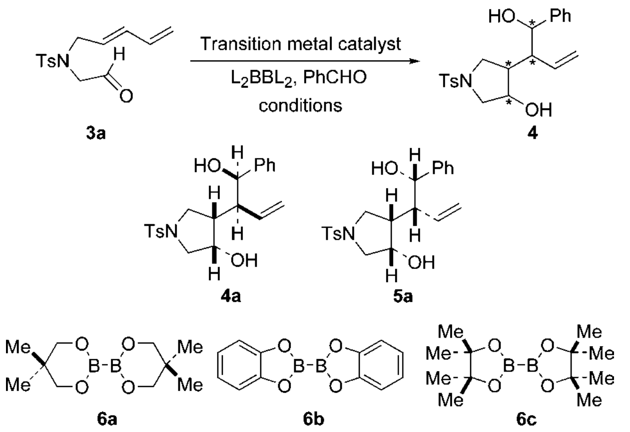
be obtained via a reductive π-allyl complex formation and a diboration from diene promoted by transition metal catalysis, respectively.

Carbonyl addition reactions of 1,3-dienes in the presence of proper reagents using nickel catalyst[5] has been intensively studied by Mori,[6] Tamaru,[7] and Ito.[8] A variety of reagents have been utilized with silans, trialkylboranes, diethyl zinc, Dibal, and disilane. To the best of our knowledge, the utilization of a diboronyl reagent (L_2BBL_2) to form **A** in Scheme 1 has not been investigated.

After early studies on the use of a diboronyl reagent to accomplish the addition to alkyne catalyzed by a platinum complex reported by Miyaura,[9] many research groups have made important contributions to the extension of this protocol to the diborations of alkenes,[10] alkynes,[11] dienes,[12] and allenes[13] for various synthetic purposes. Recently, a useful reaction of diboronyl reagent with alkenes using chiral Rh^I complexes leading to various asymmetric chemical transformations including carbohydroboration and dihydroxylation by oxidation has been reported.[14] However, the utilization of **B** as an intermediate for the sequential allylation with two aldehydes has not been reported.[16]

The realization of an efficient method for the sequential allylic transfer achieving multiple stereoselectivity should be valuable because synthetic application can be foreseen for the products.[15] We outline herein our discovery of a general and useful method in the construction of four contiguous stereogenic centers in a single operation by sequential allylic transfers to two different aldehydes. This highly steroselective transformation involves the nickel-catalyzed metalloboration to form a reactive intermediate **A**, intramolecular allylic transfer reaction to form the cyclic system, and 2-alkenylboration with an external aldehyde.

Scheme 2



To investigate the sequence outlined in Scheme 2, we began with **3a** as a starting material; we planned that the sequential carbonyl addition could be performed through intra- and intermolecular reactions. Initial attempts of a reaction of **3a** with benzaldehyde and diboronyl reagent **6** in the presence of transition metal complexes mainly employed for the diboration of an unsaturated bond[8] indicated that the conversion to the desired **4** could not be satisfied with platinum, palladium, and rhodium complexes under various reaction conditions. Even though the control experiments with styrene worked well, surprisingly, the starting **3a** remained in most cases. Subsequently we considered that other transition metal complexes might be suitable catalysts to promote this chemical transformation. After surveying numerous conditions with several transition metal complexes, we were delighted to discover that the use of Ni^0 complex led to the best results in terms of reactivity and stereoselectivity. The key findings are summarized as follows: (1) We observed a remarkable ligand effect to increase the catalytic ability; a 1:2 mixture of $Ni(cod)_2$ with P(2-furyl)$_3$ proved to be the most effective catalytic system. (2) The use of 5 mol % of catalyst turned out to be optimal in terms of chemical yields. (2) The use of other phosphine ligands including PPh_3,

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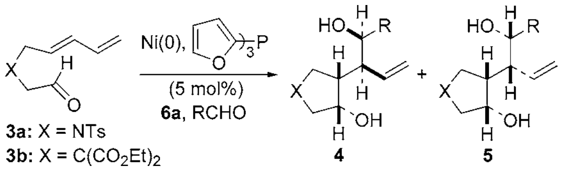
(16) For an example of the generation of multiple stereogenic centers in one operation, see: Halland, N. H.; Aburel, P. S.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1272−1277 and references therein.

P(*o*-tolyl)$_3$, PBu$_3$, and P(*c*-hexyl)$_3$ turned out to be unpromising mainly due to a lack of reactivity: none or only trace amounts (less than 10%) of products was formed. (3) Reagent **6a** was generally superior to other diboronyl reagents including **6b** and **6c**. (4) The reaction performed in THF resulted in optimum chemical yields in comparison with other solvents such as toluene, CH_3CN, and DMF.

Under optimal conditions, the reaction was conducted by a dropwise addition of **3a** (1 equiv) in THF followed by benzaldehyde (1.1 equiv) at 20 °C to a resulting solution of Ni(COD)$_2$ (0.05 equiv), P(2-furyl)$_3$ (0.1 equiv), and **6a** (1.1 equiv) in THF. After 12 h at 20 °C, workup and chromatography afforded **4a** as a sole product in 87% yield (entry 1 in Table 1; method A). It is notable that this condition affords the best yield and stereoselectivity, whereas higher temperatures, especially over 40 °C, resulted in the formation of diastereomeric products. We were surprised to find that the formation of **5a** was observed by varying the reaction temperature. After the reaction of **3a** with **6a** and subsequent intramolecular allylation under the identical conditions, the reaction mixture was cooled to −78 °C, and then benzaldehyde was added. Compound **5a** was obtained as a single adduct without the formation of any trace of **4a** (entry 2 in Table 1, method B). The relative configurations of **4a** and **5a** were unambiguously established by X-ray crystallography (see Supporting Information). It is interesting to note that the structural difference between **4a** and **5a** turned out to be a reversal of configurations of the side chain being established in the (*E*)-allkenylboration with benzaldehyde.

Table 1. Sequential Allylic Transfer Reaction of **3** with Aldehydes



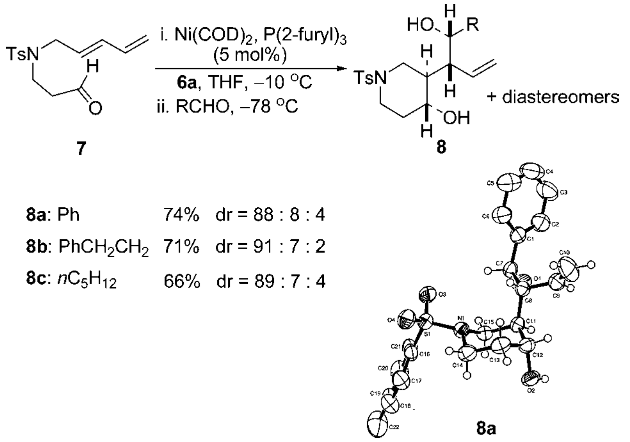
3a: X = NTs
3b: X = C(CO$_2$Et)$_2$

entry	3	RCHO	method[a]	4:5[b]	yield, %[c]
1	**3a**	Ph	A	**4a** only	87
2	**3a**	Ph	B	**5a** only	77
3	**3a**	$PhCH_2CH_2$	A	89:11	76
4	**3a**	$PhCH_2CH_2$	B	9:91	68
5	**3a**	n-C_5H_{11}	A	86:14	72
6	**3a**	n-C_5H_{11}	B	11:89	77
7	**3b**	Ph	A	95:5	85
8	**3b**	Ph	B	9:91	78
9	**3b**	$PhCH_2CH_2$	A	88:12	74
10	**3b**	$PhCH_2CH_2$	B	13:87	88
11	**3b**	n-C_5H_{11}	A	90:10	72
12	**3b**	n-C_5H_{11}	B	12:88	71

[a] Method A: reaction performed at 20 °C. Method B: reaction performed at 20 °C for 5 h and subsequent intramolecular allylation, and then intermolecular allylation with aldehyde was carried out at −78 °C. For more details, see Supporting Information. [b] Determined by ^{1}H NMR spectra of crude products and isolation of each product. [c] Yields refer to isolated and combined yields.

In light of the above results for the stereoselective sequential allylic transfer reaction depending on reaction conditions, we next turned our attention to the application of this approach with **7** to extend to the synthesis of six-membered rings. Unfortunately, the reaction of **7** with benzaldehyde under the same conditions as described in method A in Table 1 gave three diastereomers in 67% yield with an approximately 3:1:1 mixture as judged by 500 MHz ^{1}H NMR of the crude reaction mixture. Under method B in Table 1, the reaction was shown to produce the same products but different minor products ratio in a 3:1.5:0.5 mixture. Thus, to find optimum conditions a series of experiments was performed with **7**. Eventually, distereoselectivities could be improved up to 10:1 as shown in Scheme 3. The sequential allylic transfer reaction was carried out with **7** and **6a** in the presence of Ni complex at −10 °C. After 8 h at −10 °C, the resulting mixture was cooled to −78 °C, and then benzaldehyde was added. After an additional 12 h at −78 °C, the reaction was quenched. Major product **8a** was isolated in pure form by flash column chromatography, but the mixture of minor diasteromers could not be separated. The structure of **8a** was confirmed by single X-ray crystallography. The results with several aldehydes are summarized in Scheme 3. It is worthy of note that the relative stereochemistry of **8a** is well-matched with that of **4a** except for the hydroxy group in the ring. However, the temperature effect to influence a reversal of π-facial diastereoselectivity has not been observed.

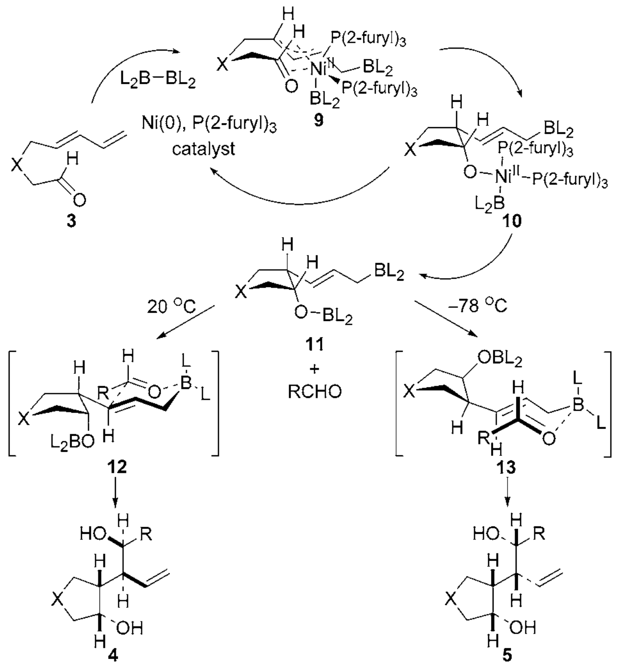
Scheme 3



8a: Ph 74% dr = 88 : 8 : 4
8b: $PhCH_2CH_2$ 71% dr = 91 : 7 : 2
8c: nC_5H_{12} 66% dr = 89 : 7 : 4

Although the exact mechanistic aspects of this transformation have not been rigorously elucidated, the following pathway could be a probable stereochemical route on the basis of product formation and our observations as illustrated in Scheme 4. As already discussed in Scheme 1, two possible intermediates, A and B, could be operative for the intramolecular allylic transfer reactions. However, intermediate B might be unlikely because the diboration with styrene under same conditions followed by oxidation with H_2O_2 gave only trace amounts of the corresponding diol. Therefore, this transformation could be promoted by the formation of π-allyl

Scheme 4



complex **9** as first proposed by Mori.[6] Following chemical routes could be probable as shown in Scheme 4: (1) reaction is promoted by oxidative addition of Ni catalyst to the diboronyl reagent **6**; (2) metalloboration with the diene **3** to give the π-allyl complex **9**; (3) subsequent carbonyl insertion to form **10**; (4) intermolecular allylic transfer reaction of **11** with aldehyde to give final products. Based on the stereochemistry of products, the intermediate **11** must be formed with regiochemical and (*E*)-alkenyl geometrical specificity. The stereochemical courses for the intra- and intermolecular allylations are predictable on the basis of previous investigations[4,5] and the well-documented (*E*)-2-alkenylborations.[2] However, the origin of remote stereocontrol of intermolecular allylation by the existing moiety to impart π-facial selectivity of the incoming aldehyde depending on reaction temperature is not clear at this moment. Since allylation would lead to the product **4a** or **5a** via stereochemical models **12** or **13** (exo to the ring), the major reaction pathway could be dependent on the stability in the transition state under a kinetic control such as orientation and steric factors offered by existing substituents: subtle geometrical preference of **12** at 20 °C and **13** at −78 °C for a minimum strain with existing components as depicted in Scheme 4.

In summary, we have developed the nickel-catalyzed sequential allylic transfer reaction of a diene with two aldehydes to establish four contiguous stereogenic centers in one operation. This highly regio- and stereocontrolled protocol involves the nickel-catalyzed metalloboration of diene, the intramolecular allylation in the construction cyclic system, and the intermolecular crotylboration of aldehydes. In each case, the observed products indicate that the sterochemical outcomes of this transformation depend on the reaction conditions. The method is extended to the synthesis of six-membered rings with up to 10:1 diastereomeric ratio. The stereochemical relationships of products are unambiguously established by single X-ray crystallography. Further studies including an asymmetric version incorporating chiral ligands are currently underway.

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Supporting Information Available: General experimental procedure details and characterization data for all products; crystal structures of **4a**, **5a**, and **8a** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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