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Asymmetric Addition of Alkenylstannanes to Alkylidene Meldrum's Acids

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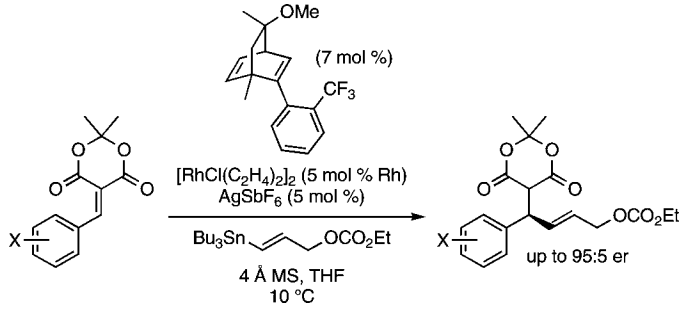
ABSTRACT



Herein, we describe enantioselective addition of alkenyltin reagents possessing a reactive and sensitive allylic functionality not readily available to other classes of alkenyl metals. This method is enabled by the use of highly electrophilic alkylidene Meldrum's acids as acceptors and a cationic Rh(I)−diene complex as catalyst.

Enantioselective conjugate additions catalyzed by chiral Rh(I) complexes have emerged as a powerful synthetic tool over the past decade.[1] Construction of new sp^3-sp^2 C−C bonds by addition of alkenylmetals to unsaturated carbonyl acceptors has been realized from silanes,[2] trifluoroborates,[3] and especially boronic acids.[4] Surprisingly, enantioselective conjugate additions employing vinylstannanes have not been reported, despite the potential utility of these pronucleophiles.[5] The advantages of working with alkenyltin reagents include their air and moisture stability, certain stoichiometry,[6] and mild syntheses of both terminal (*E*)[7] and (*Z*)[8] isomers, as well as internal,[9] vinylstannanes from simple alkyne precursors. Their relatively low reactivity also enables the preparation of alkenylstannanes bearing sensitive functional groups that may not be compatible with either the Lewis base activation of silane reagents or the aqueous solvent typically required for boronic acids. Further, mild reaction

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(3) (a) Gendrineau, T.; Genêt, J.-P.; Darses, S. *Org. Lett.* **2009**, *11*, 3486–3489. (b) Lalic, G.; Corey, E. J. *Tetrahedron Lett.* **2008**, *49*, 4894–4896. (c) Lalic, G.; Corey, E. J. *Org. Lett.* **2007**, *9*, 4921–4923. (d) Pucheault, M.; Darses, S.; Genêt, J.-P. *Eur. J. Org. Chem.* **2002**, 3552–3557.

(4) For representative recent examples, see: (a) Shintani, R.; Ichikawa, Y.; Takatsu, K.; Chen, F.; Hayashi, T. *J. Org. Chem.* **2009**, *74*, 869–873. (b) Konno, T.; Tanaka, T.; Miyabe, T.; Morigaki, A.; Ishihara, T. *Tetrahedron Lett.* **2008**, *49*, 2106–2110. (c) Zigterman, J. L.; Woo, J. C. S.; Walker, S. D.; Tedrow, J. S.; Borths, C. J.; Bunel, E. E.; Faul, M. M. *J. Org. Chem.* **2007**, *72*, 8870–8876. (d) Mauleon, P.; Carretero, J. C. *Chem. Commun.* **2005**, 4961–4963.

(5) There is only a single example of enantioselective conjugate addition employing organostannanes and Rh(I) catalysis, in which $PhSnMe_3$ was used as nucleophile; see ref 14a.

(6) Dehydration of boronic acids can make determination of their exact composition difficult: Hall, D. G. In *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH, Weinheim, Germany, 2005; pp 1−99.

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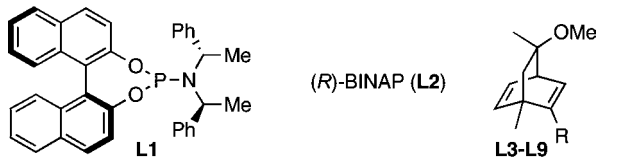
conditions compatible with sensitive functional groups on the *nucleophile* would also permit expansion in the scope of available *electrophiles*.

In this regard, we have previously reported the use of alkylidene Meldrum's acids **1** as acceptors for the racemic addition of functionalized alkenylstannanes,[10] as well as a variety of other nucleophiles under nonchiral[11] or enantioselective catalysis.[12] In this Letter, we describe the first examples of enantioselective conjugate alkenylation employing 3-(tributylstannyl)allyl carbonates and alkylidene Meldrum's acids, reactions that take place at low temperature under mild and anhydrous conditions.

Cognizant that the low reactivity of the C−Sn bond presents a barrier to transmetalation, ligand selection was a crucial consideration (Figure 1).



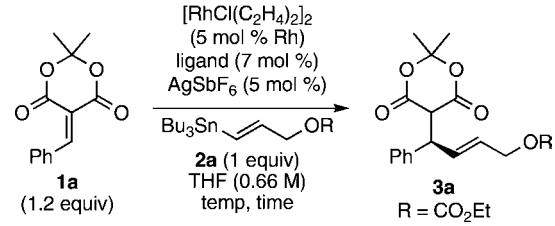
R = C_6H_5 (**L3**), 2-MeC_6H_4 (**L4**), 2,6-$(Me)_2C_6H_3$ (**L5**), 9-anthracene (**L6**), 2-*i*PrC_6H_4 (**L7**), 2-$CF_3C_6H_4$ (**L8**), 2-CF_3-4-$OMeC_6H_3$ (**L9**)

Figure 1. Chiral ligands for asymmetric conjugate addition.

Initial attempts using a $[Rh(C_2H_4)_2Cl]_2$ precatalyst in the presence of phosphoramidite **L1** and (*R*)-BINAP (**L2**) left the starting materials unchanged and yielded no desired product (Table 1, entries 1 and 2, respectively). Fortunately, chiral diene ligands have recently emerged as a complementary alternative to privileged phosphine scaffolds as a way of overcoming low catalytic activity while maintaining high enantioselectivity.[13,14] Employing known and easily prepared C_1-symmetric chiral diene **L3**[14b] furnished the desired product with excellent conversion and an encouraging 61:39 er (entry 3). While introduction of an *ortho*-substituent (**L4**, entry 4) provided an increase in selectivity, the more interesting finding was the large gain in er observed upon addition of $AgSbF_6$ to sequester the chloride ion from the Rh(I) complex (entry 5). Continuing under these cationic conditions, it was found that while decreasing the temperature provides increased selectivity, it does so at the eventual expense of conversion (entries 6−8). Known ligand **L5**, which has been found more effective than **L3** and **L4** in other systems,[14d] and new, 9-anthracenyl-containing **L6**, both of which have two *ortho*-substituents, were poorly or not at all reactive (entries 9 and 10, respectively).

Taking these results into consideration, it was apparent that the optimal mix of selectivity and conversion would come from a ligand bearing an arene with a single, large group at the *ortho* position. New ligands **L7**, **L8**, and **L9** were prepared, and all proved to be more selective than **L4** and to give higher conversion than **L5** (entries 11−15). Trifluoromethylated ligand **L8** was settled upon as the ligand of choice on the basis of its slight superiority in terms of enantioselectivity and its higher yielding synthesis from inexpensive starting material.[15] Finally, introduction of

Table 1. Survey of Chiral Ligands and Optimization



entry	ligand	temp (°C)	time (h)	conversion (%)	er
1[a]	**L1**	rt	24	0	
2[a]	**L2**	rt	24	0	
3[a]	**L3**	rt	24	>99	61:39
4[a]	**L4**	rt	24	>99	71:29
5	**L4**	rt	24	>99	88:12
6	**L4**	0	37	>99	91:9
7	**L4**	−10	24	37	93:7
8	**L4**	−20	24	20	93:7
9	**L5**	0	46	23	94:6
10	**L6**	0	45	0	
11	**L7**	0	46	>99	93:7
12	**L8**	0	45	51	95:5
13[b]	**L8**	10	45	>99	93:7
14	**L8**	rt	45	>99	91:9
15	**L9**	10	45	>99	92:8
16[c]	**L8**	10	45	>99	94:6

[a] Entries 1−4 performed without $AgSbF_6$. [b] 66% isolated yield. [c] 4 Å molecular sieves added; isolated yield 84%.

(7) By Pd-catalyzed hydrostannation: (a) Darwish, A.; Lang, A.; Kim, T.; Chong, J. M. *Org. Lett.* **2008**, *10*, 861–864. (b) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857–1867. By radical hydrostannation: (c) Nozaki, K.; Oshima, K.; Uchimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547–2549.

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(9) Kazmaier, U.; Schauss, D.; Pohlman, M. *Org. Lett.* **1999**, *1*, 1017–1019.

(10) Fillion, E.; Carret, S.; Mercier, L. G.; Trépanier, V. É. *Org. Lett.* **2008**, *10*, 437–440.

(11) (a) Mahoney, S. J.; Moon, D. T.; Hollinger, J. A.; Fillion, E. *Tetrahedron Lett.* **2009**, *50*, 4706–4709. (b) Dumas, A. M.; Fillion, E. *Org. Lett.* **2009**, *11*, 1919–1922. (c) Fillion, E.; Dumas, A. M.; Kuropatwa, B. A.; Malhotra, N. R.; Silter, T. C. *J. Org. Chem.* **2006**, *71*, 409–412.

(12) (a) Fillion, E.; Zorzitto, A. K. *J. Am. Chem. Soc.* **2009**, *131*, 14608–14609. (b) Wilsily, A.; Lou, T.; Fillion, E. *Synthesis* **2009**, 2066–2072. (c) Wilsily, A.; Fillion, E. *Org. Lett.* **2008**, *10*, 2801–2804. (d) Fillion, E.; Wilsily, A. *J. Am. Chem. Soc.* **2006**, *128*, 2774–2775.

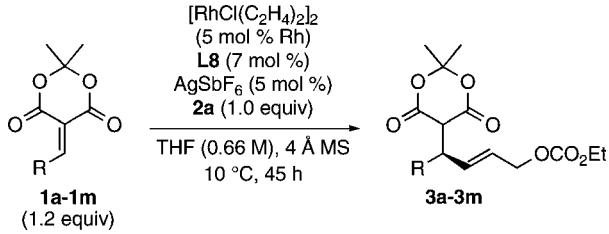
(13) Defieber, C.; Grützmacher, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4482–4502.

(14) For examples representative of the variety of available chiral diene ligands, see refs 2f and 4a as well as: (a) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508–11509. (b) Fisher, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628–1629. (c) Paquin, J.-F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 10850–10851. (d) Gendrineau, T.; Chuzel, O.; Eijberg, H.; Genêt, J.-P.; Darses, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7669–7672. (e) Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336–5337. (f) Okamoto, K.; Hayashi, T.; Rawal, V. H. *Chem. Commun.* **2009**, 4815–4817. (g) Hu, X.; Zhuang, M.; Cao, Z.; Du, H. *Org. Lett.* **2009**, *11*, 4744–4747.

powdered molecular sieves was found to be crucial to prevent hydrolysis of the alkylidene leading to cleaner reactions and higher isolated yields (entry 16).

It was found that the addition of **2a** was general to a number of substituted alkylidene Meldrum's acids (Table 2),

Table 2. Asymmetric Addition to Alkylidene Meldrum's Acids using **L8**[a]



entry	R	yield (%)	er[b]
1	C_6H_5 (**1a**)	84 (**3a**)	94:6
2	2-(OMe)C_6H_4 (**1b**)	58 (**3b**)	92:8
3	3-(OMe)C_6H_4 (**1c**)	54 (**3c**)	91:9
4	3-MeC_6H_4 (**1d**)	51 (**3d**)	93:7
5	3-(Bpin)C_6H_4 (**1e**)	57 (**3e**)	93:7
6	3-BrC_6H_4 (**1f**)	70 (**3f**)	95:5
7	4-(OMe)C_6H_4 (**1g**)	17 (**3g**)	93:7
8	4-MeC_6H_4 (**1h**)	42 (**3h**)	93:7
9	4-(Bpin)C_6H_4 (**1i**)	39 (**3i**)	93:7
10	4-BrC_6H_4 (**1j**)	39 (**3j**)	93:7
11[c]	4-ClC_6H_4 (**1k**)	29 (**3k**)	90:10
12[c]	2-naphthyl (**1l**)	49 (**3l**)	92:8
13	Me (**1m**)	73 (**3m**)	77:23

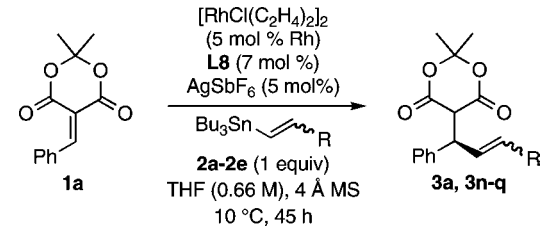
[a] Reactions performed as in Table 1, entry 16. [b] Absolute configuration assigned by analogy to a derivative of **3h**; see Supporting Information. [c] Final concentration of **1** was 0.4 M.

proceeding in comparable enantioselectivity regardless of the nature of the substituent on the phenyl ring. Substitution was possible at the *ortho*, *meta*, and *para* positions (entries 2, 3, and 7, respectively), and the reaction tolerated aryl halides (entries 6, 10, and 11) and even boronic esters (entries 5 and 9). The latter two examples highlight the mild nature of these additions, while providing the potential for orthogonal reactivity of different C-M bonds in Rh(I)-catalyzed conjugate additions. In some cases the highly concentrated conditions required for good conversion led to low solubility of the electrophile, and slight dilution provided a compromise between reaction rate and homogeneous solution (entries 11 and 12). Nonaryl alkylidene **1m** reacted with relatively good yield but substantially lower selectivity (entry 13).

Addition of other alkenylstannanes was also successful, although none matched carbonate **2a** in enantioselectivity. The allyl acetate containing tin reagent **2b** gave the addition product in slighly lower yield (Table 3, entry 2). Facile introduction of either allylic carbonate or acetates provides a useful complement in further transformations, particularly in Pd-catalyzed allylic substitutions. Addition of the (*Z*)-

(15) See Supporting Information for details.

Table 3. Enantioselective Addition of Alkenylstannanes to Alkylidene Meldrum's Acid **1a**



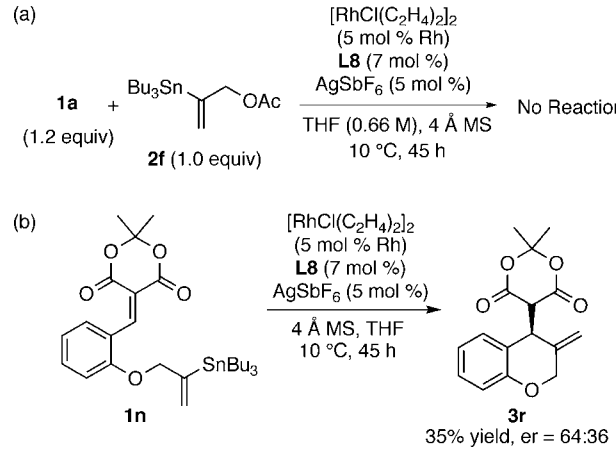
entry	R	yield (%)	er
1	(*E*)-CH_2OCO_2Et (**2a**)	84 (**3a**)	94:6
2	(*E*)-CH_2OAc (**2b**)	61 (**3n**)	89:11
3	(*Z*)-CH_2OAc (**2c**)	87 (**3o**)	83:17
4	H (**2d**)	ND[a] (**3p**)	63:37
5	(*E*)-CO_2Et (**2e**)	NR (**3q**)	

[a] Product **3p** was inseparable from excess alkylidene **1a**; see Supporting Information for details.

isomer **2c** proceeded with full retention of double bond geometry, leading to (*Z*)-**3o**. As also observed in racemic reactions,[10] addition of unfunctionalized vinylstannanes was considerably slower, and **2d** gave low conversion and selectivity. The accelerating effects of the allylic functionality in **2a**−**2c** does not appear to be caused solely by electron withdrawal by the adjacent oxygen atom, as alkenylstannane **2e** gave no conversion.

In contrast to terminal alkenyltins **2a**−**c**, geminal stannane **2f** proved resistant to conjugate addition (Scheme 1a). In

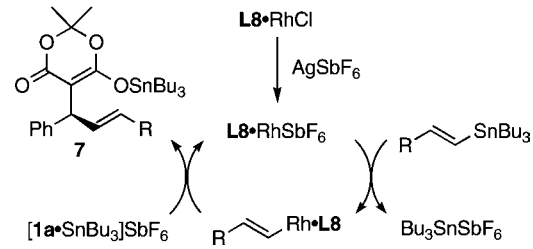
Scheme 1. Inter- and Intramolecular Reactions of Geminal Alkenyl Stannanes



order to facilitate this difficult reaction, alkylidene Meldrum's acid **1n** was prepared to allow intramolecular cyclization. Under the conditions optimized for intermolecular reactions, Meldrum's acid **3r** was obtained in low yield and 64:36 er, without isomerization of the sensitive exomethylene group (Scheme 1b).

As mentioned, Rh(I)-catalyzed additions of boronic acids are performed under basic, protic conditions partially in order to activate the boronic acid by formation of an intermediate borate.[16] Additionally, as demonstrated in detailed studies by Hayashi, these reactions proceed by formation of an oxa-π-allyl Rh(I) complex that is protonated by the cosolvent (often H_2O or MeOH) to turn over the catalyst.[17] On the other hand, the addition of alkenylstannanes we have described is best performed under cationic and anhydrous conditions.[18] Taking into account the significant increase in enantioselectivity observed by introduction of $AgSbF_6$ to remove chloride from the Rh(I) precatalyst, we propose the mechanism outlined in Scheme 2. Here, transmetalation between Rh and the alkenylstannane forms the active nucleophile while generating a cationic Sn species, which can act as a Lewis acid. Complexation of **1a** to Sn activates the electrophile and leads directly to the stable Sn-enolate **7** upon addition of the alkenyl rhodium.[19] Significantly, a similar cooperative mechanism has recently been proposed in the additions of tetraarylborates to cycloalkenones,[20] and this concept may open avenues for further improvements to our method.

Scheme 2. Proposed Mechanism for Enantioselective Conjugate Alkenylation



In conclusion, we have described the first examples of inter- and intramolecular enantioselective conjugate alkenylations employing organostannanes. The unique conditions required for the alkenylation make this process complementary to existing protocols employing other alkenylmetals. Further work to fully elucidate the mechanism and apply these conditions to other tin-based nucleophiles to expand the reaction scope is in progess.

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

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