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## Palladium-catalyzed regiocontrolled and stereoselective alkylations of bis(trifluoroethyl) malonates with dienyl alcohols<sup> $\Rightarrow$ </sup>

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**Abstract**—The triethylborane-promoted and palladium-catalyzed reactions of 2,4-dienyl alcohols or the corresponding isomeric divinyl alcohols with bis(trifluoroethyl) malonates provide an improved method for the regio- and stereoselective dienylation of malonates. The phosphine ligand is an important control element in the reaction. Combinations of  $Pd(OAc)_2$  with BIPHEP or BINAP give dienylated malonates in good yield and higher isomeric purity than the traditional combination of  $Pd(OAc)_2$  and  $Ph_3P$  affords in the catalyzed reactions of dienyl acetates.

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Methods for the stereoselective preparation of substituted 1,3-dienes are of interest due to their presence within the structures of natural products and their use as substrates for cycloaddition reactions and a variety of metal-catalyzed reactions. We are particularly interested in the latter topic,<sup>1</sup> and consequently, seek simple, practical methods for introducing the 1,3-diene moiety with good regio- and stereochemical control. Toward this end, we have developed and refined several dienylation methods.<sup>2–4</sup>

Transition metal catalyzed alkylations of malonates and related pronucleophiles by dienyl acetates and carbonates represents a rather simple and direct method for dienylation, and as such, these methodologies have been quite extensively investigated. The reaction is com-



**Figure 1.** The problems of regio- and stereochemical control in malonate dienylations.

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plicated by the fact that the diene substrate presents three potential sites for alkylation. Considering even a relatively simple diene, for example, the 5-substituted-2,4-dienyl acetate illustrated in Figure 1, alkylation at any of the three sites can potentially give rise to two or more stereoisomers. In the example illustrated, eight isomers are possible from the dienylation reaction. For our purposes, we are particularly interested in obtaining the product of alkylation at the  $\alpha$ -position with good control of diene geometry (i.e. (E,E)-1).

Improving the regiocontrol and stereoselectivity of metal-catalyzed dienylations has been recognized as an important goal, and a number of mechanistic and synthetic studies have been reported. Most studies focus on one or more of the following factors, the effect of substituents on the diene substrate and its substitution pattern,<sup>5–9</sup> the nature of the nucleophile and its counterion,<sup>10</sup> or the choice of metal and ligand. Catalysts systems derived from tungsten,<sup>9</sup> molybdenum,<sup>11</sup> and iridium<sup>12</sup> tend to give predominantly the product of internal alkylation, that is, addition to the  $\gamma$ -position illustrated in Figure 1 and afford a divinyl alcohol, rather than conjugated diene, as the major product.

Dienylations catalyzed by palladium are strongly influenced by the nature of the ligand.<sup>13,14</sup> Those modified by PPh<sub>3</sub> generally give a mixture of products with the predominant one derived from addition to the  $\alpha$ -position. For example, the palladium-catalyzed dienylation of diethyl methylmalonate (2) by 2,4-hexadienyl acetate (3) proceeds in high yield, but affords a mixture of products 4 (70%) and 5 (30%) resulting from competing

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substitution at the  $\alpha$ - and  $\gamma$ -positions (Scheme 1). Control over the alkene geometry in the diene derived from each mode is usually good (>95% *E*). The alkylation is reversible at elevated temperature with palladium catalysts that use PBu<sub>3</sub> as the ligand. Dienylation under these conditions increases the percentage of **4**, but suffers from the erosion of its stereoisomeric purity. The product mixture typically contains only 70–90% of the (*E*,*E*)-isomer of **4**.<sup>13</sup>



Scheme 1. Results typical of those obtained for the palladium-catalyzed alkylation of malonates by dienyl acetates.

Recently, Tamaru and co-workers reported the  $Et_3B$ promoted reaction of allyl alcohols in palladium-catalyzed allylations of active methylene compounds,<sup>15</sup> and other pronucleophiles.<sup>16–18</sup> Their report included one promising malonate dienylation reaction, and we therefore decided to further explore the scope of the reaction. Our study led to the development of an alternative malonate substrate and a modified catalyst system that provides an improved method for the regio- and stereoselective dienylations of malonates. Via this new procedure, dienylated malonates are obtained in higher isomeric purity than typically observed for palladiumcatalyzed reactions of dienyl acetates.

Bis(trifluoroethyl) malonates are more acidic than the corresponding diethyl malonates, and as a consequence, exhibit subtle differences in their alkylation chemistry. For example, as carbon nucleophiles, bis(trifluoroethyl) malonates participate more readily than the corresponding diethyl derivatives in Mitsunobu alkylation reactions.<sup>19</sup> We decided to explore their use in dienylation reactions and find that treating a mixture of the sodium salt of bis(trifluoroethyl) methylmalonate (**6**) with an equivalent of 2,4-hexadien-1-ol (**7**), 1.2 equiv. of triethylborane, 0.1 equiv. of Pd(OAc)<sub>2</sub> and a phos-



Scheme 2. The  $Et_3B$ -promoted and palladium-catalyzed reaction of bis(trifluoroethyl) malonate 6 with 2,4-hexadien-1-ol (7).

phine ligand (THF, 25°C, 12 h) affords dienylated products in good yield (Scheme 2).

A broad range of ligands have been examined in palladium-catalyzed allylation reactions, and the choice of ligand has been shown to substantially influence the regio- and stereochemical outcome of the addition.<sup>20–22</sup> A variety of phosphine ligands were screened in the dienylation reaction illustrated in Scheme 2. In each case, the reaction was found to be highly regioselective for substitution at the  $\alpha$ -position, but inevitably formed a mixture of stereoisomers. As summarized in Table 1,<sup>†</sup> the isomer ratio is strongly dependent on the ligand

Table 1. The influence of ligands on the yield and stereoselectivity for the formation of 8 under the conditions of Scheme  $2^a$ 

Entry	Ligand <sup>b</sup>	(E,E)- <b>8</b> (%)	8′ (%)	8″ (%)
1	PPh <sub>3</sub>	57	13	6
2	dppe	47	13	15
3	dppp	56	15	11
4	dppb	55	18	13
5	dppf	54	17	10
6	XANTPHOS	46	20	6
7°	BIPHEP	92	4	4
8°	rac-BINAP	88	6	6

<sup>a</sup> The reported yields were determined by analysis of the <sup>1</sup>H NMR spectrum of the crude reaction mixture. See the representative procedure<sup>†</sup> for the experimental details.

- <sup>b</sup> 1 equiv. of ligand was employed, except in the case of  $Ph_3P$  where 2 equiv. were added.
- <sup>c</sup> The isolated product is obtained in 89% yield and is 93% the (E,E)-isomer using BIPHEP and in 80% yield (92% (E,E)) using BINAP.
- <sup>†</sup> Representative procedure: To a nitrogen blanketed solution (ca. 25°C) of bis(trifluoroethyl) methylmalonate (100 mg, 0.36 mmol) and 2,4-hexadien-1-ol (7) (35 mg, 0.36 mmol) in THF (1 mL) was added NaH (9.4 mg, 0.39 mmol). The resulting mixture was stirred until the NaH was consumed (ca. 15 min). In a separate flask, a mixture of Pd(OAc)<sub>2</sub> (8.0 mg, 0.036 mmol) and either rac-BINAP (23.5 mg, 0.036 mmol) or BIPHEP (18.6 mg, 0.036 mmol) was stirred in THF (2 mL, 10 min). (Note: An orange precipitate typically forms in the case of BINAP, and occasionally, a precipitate forms with BIPHEP.) The substrate mixture was added to the Pd(OAc)<sub>2</sub> mixture, followed by the addition of Et<sub>3</sub>B (1 M in hexanes, 0.43 mL, 0.43 mmol). (It should be noted that this addition order was found to be important for successful reaction). The resulting homogeneous mixture was stirred overnight (ca 12 h, 25°C). Afterwards, the mixture was concentrated via rotovap and filtered through a plug of silica. (Yields reported for the stereoisomers in Table 1 are determined by analysis of the <sup>1</sup>H NMR spectrum at this stage.) In preparative experiments (vide infra), the residue was purified by chromatography on silica (1% ether in hexane) to afford compound 8 (115 mg (89%) in the case of BIPHEP and 103 mg (80%) in the case of BINAP): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, major isomer):  $\delta$  6.02-6.07 (m, 1H), 5.93-5.99 (m, 1H), 5.58-5.65 (m, 1H), 5.34-5.52 (m, 1H), 4.44-4.50 (m, 4H), 2.65 (d, 7.2 Hz, 2H), 1.66 (d, 7.1 Hz, 3H), 1.47 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 169.6, 135.7, 130.8, 129.5, 122.7, 122.5 (q, 275.3) Hz), 60.9 (q, 36.7 Hz), 54.0, 38.8, 19.6, 17.9; IR (neat): 2978, 2331, 1731, 1452, 1378, 1021, 968, 852, 747 cm<sup>-1</sup>; MS (m/z): 362 (M<sup>+</sup>), 234, 107, 81 (100); HRMS calcd for C14H16F6O4 (M+) 362.0963, found 362.0946.

A. The reaction of 6 with 7 (L = BIPHEP).



C. Reaction of diethyl methylmalonate anion 2 with 7 ( $L = PPh_3$ , n = 2).



**Figure 2.** Comparing the isomer distribution obtained under the conditions described in Scheme 2 and Table 1, regions of the crude <sup>1</sup>H NMR spectra showing peaks due to (E,E)-8 (H<sup>a</sup>), its (Z)-isomers 8' (H<sup>a'</sup>) and 8 (H<sup>a''</sup>), and due to (E,E)-4 (H<sup>a</sup>) and its stereoisomers (H<sup>a'</sup>, H<sup>a''</sup>) and 5 (H<sup>b</sup>).

used. For example, PPh<sub>3</sub> (entry 1) gives a relatively modest level of stereoselectivity, just 3:1 favoring the (E,E)-8 isomer over (Z)-isomers.

The ligand–metal–ligand angle (bite angle) of bidentate ligands<sup>23</sup> has been found to play an important role in controlling regio- and stereoselectivity in palladium-catalyzed allylations. For example, van Leeuween and co-workers found that the percentage of (*E*)-isomer obtained from allylation increased for the ligands dppe, dppp, dppb, dppf and sixantphos, a series of chelating ligands that span the range of bite angles from ca. 85° to 109°.<sup>24</sup> A similar series was examined in the dienylation reaction (i.e. Table 1, entries 2–5 and entry 6 (xantphos)), but we do not see a similar correlation with the yield of (*E*,*E*)-8. Nonetheless, two of the ligands screened, BIPHEP (2,2'-bis(diphenylphosphino)-1,1'-biphenyl)<sup>25</sup> and BINAP (entries 7 and 8), proved superior to the others.

The data in Table 1 are based on NMR analysis of the crude reaction mixture. Figure 2 shows the relevant regions of the <sup>1</sup>H NMR spectra. Figure 2A shows peaks due to (E,E)-8 (H<sup>a</sup>) and its (Z)-isomers 8' (H<sup>a'</sup>) and 8" (H<sup>a''</sup>) and is obtained on the crude product prepared using BIPHEP. For comparison, Figure 2B shows the less favorable mixture obtained using Ph<sub>3</sub>P (2 equiv.) under otherwise identical conditions, and Figure 2C shows the reaction mixture obtained under the Ph<sub>3</sub>P conditions when the diethyl methylmalonate anion (2) is used in place of the bis(trifluoroethyl) derivative 6. The latter spectrum shows the regioisomeric divinyl product 5 is present in substantial amount, while in comparison that isomer is not observed with the bis(trifluoroethyl) derivative 6.

Table 2 illustrates dienylation with a range of substrates. In most cases the reaction was examined with both BIPHEP and BINAP. Typically, the differences are small. Since no new tetrahedral stereocenters are generated in the course of the dienylation, the racemate is employed in cases where BINAP is used. Both dienyl alcohols and divinyl alcohol can be used as substrates in the reaction (e.g. entries 1 and 2). In a number of cases (e.g. entries 3, 4, and 6), products containing trisubstituted double bonds formed with good to excellent control of stereochemistry. In other examples (e.g. entries 5 and 7) the level of control is only moderate. Aryl substituted dienols also show good regioselectivity in the reaction (entries 7–11).<sup>7,9</sup>

Attempted monoalkylation of the parent bis(trifluoroethyl) malonate (9) gave mostly the doubly alkylated product 10. The double dienylation can be preparatively useful as illustrated by the reaction of 9 with 2 equiv. of dienol 7 (Scheme 3).



7 (2 equivalents)

Scheme 3. The double dienylation of bis(trifluoroethyl) malonate 9.

Entry	Malonate	Dienyl or divinyl alcohol	Product	L= <i>rac</i> -BINAP yield (% E,E) <sup>b</sup>	L = BIPHEP yield (% E,E) <sup>b</sup>
1	$\begin{array}{c} F_{3}CH_{2}CO_{2}C \\ F_{3}CH_{2}CO_{2}C \\ \end{array} \begin{array}{c} H \\ CH_{2}Ph \\ 11 \end{array}$	но	E <sup>F</sup> Bn	99	83
2	11	H <sub>2</sub> C	E <sup>F</sup> Bn	84	93
3	11	H <sub>2</sub> C Me	E <sup>F</sup> Bn	74	86
4	11	HO Me Me	E <sup>F</sup> Bn Me	85 (94)	88 (95)
5	11	H <sub>2</sub> C H <sub>3</sub>	$E^{F}$ $He$ $E^{F}$ $CH_{3}$	78 (67)	69 (75)
6	11	HOME	E <sup>F</sup> Bn Me	63 (93)	61 (92)
7	11	HOME	E <sup>F</sup> Bn Me	82 (87)	70 (86)
8°	F <sub>3</sub> CH <sub>2</sub> CO <sub>2</sub> C F <sub>3</sub> CH <sub>2</sub> CO <sub>2</sub> C H T2 CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>	OH H <sub>2</sub> C CH <sub>3</sub>	E <sup>F</sup> CH <sub>3</sub>		76 (92)
9	12	OH H <sub>2</sub> C 13a (X = H)	$E^{F}$ $E^{F}$ $CH_{2}$ X 14a (X = H)	57 (84)	
10	12	13b (X = OMe)	<b>14b</b> (X = OMe)		72
11	12	$13c (X = CO_2Me)$	$14c (X = CO_2Me)$		60 (91)

Table 2. A survey of  $Et_3B$ -promoted, palladium-catalyzed alkylation of bis(trifluoroethyl)malonates with dienyl and divinyl alcohols

<sup>a</sup> Experimental details are given in the Representative Procedure and spectral characterization data for the major isomer were submitted as Supplementary Data. <sup>b</sup> Unless otherwise noted, the isomeric purity as estimated by <sup>1</sup>H NMR is 95% (E,E) or greater. The isomer ratio is essentially unchanged after purification via flash chromatography on silica under the conditions employed. <sup>c</sup> For the preparation of compound **12**, see reference 19.

In summary, Tamaru recently reported the  $Et_3B$ -promoted and palladium-catalyzed alkylation of malonates by allyl alcohols. Inspired by their work, we examined dienylations by dienyl and divinyl alcohols, and find bis(trifluoroethyl) malonate derivatives and palladium catalysts modified by BIPHEP or BINAP afford dienylated malonates with high regioselectivity and good-toexcellent stereoselectivity.

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## References

- Takacs, J. M.; Vayalakkada, S.; Mehrman, S. J.; Kingsbury, C. L. *Tetrahedron Lett.* 2002, 43, 8417–8420.
- Takacs, J. M.; Jaber, M. R.; Clement, F.; Walters, C. J. Org. Chem. 1998, 63, 6757–6760.
- Takacs, J. M.; Jaber, M. R.; Swanson, B. J.; Mehrman, S. J. *Tetrahedron: Asymmetry* **1998**, *9*, 4313– 4324. 4.Takacs, J. M.; Weidner, J. J. J. Org. Chem. **1994**, 59, 6480–6483.
- Shimizu, I.; Matsumoto, Y.; Nishikawa, M.; Kawahara, T.; Satake, A.; Yamamoto, A. *Chem. Lett.* 1998, 983– 984.
- Kang, S.-K.; Park, D.-C.; Jeon, J.-H.; Rho, H.-S.; Yu, C.-M. *Tetrahedron Lett.* 1994, *35*, 2357–2360.
- Trost, B. M.; Urch, C. J.; Hung, M. H. Tetrahedron Lett. 1986, 27, 4949–4952.
- Trost, B. M.; Lautens, M.; Hung, M. H.; Carmichael, C. S. J. Am. Chem. Soc. 1984, 106, 7641–7643.
- Trost, B. M.; Hung, M. H. J. Am. Chem. Soc. 1984, 106, 6837–6839.
- Trost, B. M.; Bunt, R. C. J. Am. Chem. Soc. 1998, 120, 70–79.
- 11. Trost, B. M.; Hildbrand, S.; Dogra, K. J. Am. Chem. Soc. 1999, 121, 10416-10417.
- 12. Takeuchi, R.; Tanabe, K. Angew. Chem., Int. Ed. 2000, 39, 1975–1978.
- Nilsson, Y. I. M.; Andersson, P. G.; Backvall, J. E. J. Am. Chem. Soc. 1993, 115, 6609–6613.

- 14. Andersson, P. G.; Backvall, J. E. J. Org. Chem. 1991, 56, 5349–5353.
- Tamaru, Y.; Horino, Y.; Araki, M.; Tanaka, S.; Kimura, M. *Tetrahedron Lett.* 2000, *41*, 5705–5709.
- Horino, Y.; Naito, M.; Kimura, M.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* 2001, 42, 3113–3116.
- Kimura, M.; Horino, Y.; Mukai, R.; Tanaka, S.; Tamaru, Y. J. Am. Chem. Soc. 2001, 123, 10401–10402.
- Kimura, M.; Futamata, M.; Shibata, K.; Tamaru, Y. Chem. Commun. 2003, 234–235.
- Takacs, J. M.; Xu, Z.; Jiang, X.-t.; Leonov, A. P.; Theriot, G. C. Org. Lett. 2002, 4, 3843–3845.
- Ogasawara, M.; Takizawa, K.-i.; Hayashi, T. Organometallics 2002, 21, 4853–4861.
- Ross, J.; Chen, W.; Xu, L.; Xiao, J. Organometallics 2001, 20, 138–142.
- van Haaren, R. J.; Druijven, C. J. M.; van Strijdonck, G. P. F.; Oevering, H.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. J. Chem. Soc., Dalton Trans. 2000, 10, 1549–1554.
- van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. Chem. Rev. 2000, 100, 2741–2769.
- van Haaren, R. J.; Oevering, H.; Coussens, B. B.; van Strijdonck, G. P. F.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Eur. J. Inorg. Chem.* **1999**, 1237– 1241.
- Ogasawara, M.; Yoshida, K.; Hayashi, T. Organometallics 2000, 19, 1567–1571.