Regioselective Rhodium-Catalyzed Allylic Linchpin Cross-Coupling Reactions: Diastereospecific Construction of *anti*-1,3-Carbon Stereogenic Centers and C_2-Symmetrical Fragments

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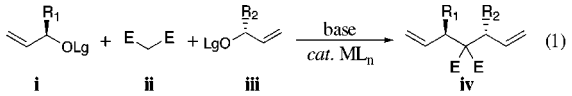
The stereocontrolled construction of acyclic *anti*-1,3-carbon stereogenic centers, including C_2-symmetrical fragments, represents a fundamentally important process for target-directed synthesis.[1] Although a variety of excellent synthetic strategies have been devised to address this problem, the ability to control 1,3-carbon stereogenic centers by using sequential enantiospecific metal-catalyzed allylic substitution reactions with *unsymmetrical* acyclic chiral nonracemic secondary allylic alcohol derivatives has not been addressed (eq 1).[2] The metal-catalyzed allylic substitution with α-substituted malonates has been examined; however, symmetrical or stereoelectronically biased substrates are required to circumvent poor regioselectivity.[3,4]



We envisioned that the rhodium-catalyzed allylic substitution reaction would facilitate this type of linchpin cross-coupling reaction owing to its propensity to undergo selective alkylation through the formation of a distorted π-allyl or *enyl* ($\sigma + \pi$) organorhodium intermediate.[5−7] Herein, we now describe the sequential regioselective and enantiospecific rhodium-catalyzed allylic alkylation of *unsymmetrical* acyclic chiral nonracemic allylic carbonates **i** and **iii** with the sodium salt of dimethyl malonate **ii** for the construction of acyclic *anti*- and C_2-*symmetrical* 1,3-carbon stereogenic centers **iv** (eq 1, $R_1 \neq R_2$ and $R_1 = R_2$).

Preliminary studies examined the feasibility of the sequential regioselective and enantiospecific metal-catalyzed allylic alkylation, with a series of stabilized carbon nucleophiles, to determine the optimum linchpin (eq 2, Table 1).[5,6e] Treatment of the secondary carbonate (*R*)-**2a** with the sodium salt of the enantiomerically enriched α-substituted malonates **1a**−**a″** under our standard allylic alkylation conditions furnished the alkylation products **3**−**5a**−**a″** in 73−95% yield (entries 1−3). The dimethyl malonate derivative **1a** (E = CO_2Me, 93% ee) proved optimum in terms of selectivity and its convenience for stereochemical analysis. Additional studies focused on the effect of the triorganophosphite additive. This study demonstrated that increasing both the cone angle and π-acidity leads to diminished selectivity (entry 1 vs 4),[8a] while significantly increasing π-acidity, with trifluoroethyl phosphite,[8b] led to optimum regioselectivity (entry 5 vs 6). The improved regioselectivity was tentatively attributed to the increased electrophilicity of the metal−allyl intermediate, thereby electronically promoting alkylation at the more substituted terminus of the allyl fragment.[2,5]

Table 1. Effect of Stabilizing Groups and Phosphite Additives on Regioselectivity and Diastereospecificity with (*R*)-**2a** (R_2 = Me, 95% ee)

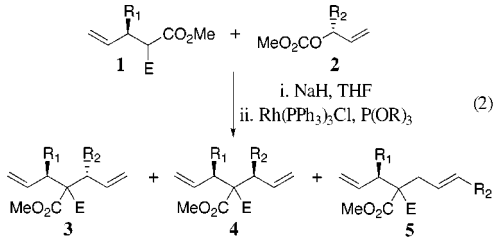
entry	Nu **1** (R_1 = Me)[a] E =	phosphite additive	2°:1° (**3**+**4**):**5**[b,c]	ds **3**:**4**[b]	yield (%)[d]
1	CO_2Me (**a**)	$P(OMe)_3$	7:1	18:1	73
2	CN (**a′**)	$P(OMe)_3$	5:1	5:1	74
3	SO_2Ph (**a″**)	$P(OMe)_3$	1:2	15:1	95
4	CO_2Me (**a**)	$P(OPh)_3$	1:1	5:1	54
5	CO_2Me (**a**)	$P(OEt)_3$	9:1	15:1	79
6	CO_2Me (**a**)	$P(OCH_2CF_3)_3$	21:1	16:1	91

[a] All reactions were carried out on a 0.2 mmol reaction scale at 30 °C in THF (0.07 M) with 1.5 equiv of **1a**−**a″** (93% ee). [b] Ratios of regio- and diastereoisomers were determined by capillary GLC on crude reaction mixtures. [c] The primary products **5** were prepared independently *via* Pd(0) catalysis.[2] [d] Isolated yields.

Table 2. Scope of the Rhodium-Catalyzed Allylic Alkylation with Enantiomerically Enriched α-Branched Malonates **1a**−**c** (93−99% ee)

entry	malonate **1** (E = CO_2Me), R_1 =[a]	carbonate **2**, R_2 =			2°:1° (**3**+**4**):**5**[b]	ds **3**:**4**[b]	yield (%)[c]
1	Me (**a**)	Me	(**a**)[9]	a	21:1	16:1	91
2	Me (**a**)	Ph	(**b**)	b	8:1	7:1	86
3	Me (**a**)	$BnOCH_2$	(**c**)	c	1:≥99[d]	ND	81
4	Ph (**b**)	Me	(**a**)	d	35:1	30:1	91
5	Ph (**b**)	Ph	(**b**)	e	8:1	39:1	88
6	Ph (**b**)	$BnOCH_2$	(**c**)	f	1:≥99[d]	ND	79
7	$BnOCH_2$ (**c**)	Me	(**a**)	g	47:1	10:1	90
8	$BnOCH_2$ (**c**)	Ph	(**b**)	h	6:1	3:1[e]	83
9	$BnOCH_2$ (**c**)	$BnOCH_2$	(**c**)	i	1:≥19[e]	ND	82

[a] All reactions were carried out on a 0.2 mmol reaction scale at 30 °C in THF (0.07 M) with 1.5 equiv of **1**. [b] Ratios of regio- and diastereoisomers were determined by capillary GLC. [c] Isolated yields. [d] ≥99:1 in favor of the (*E*)-isomer by capillary GLC. [e] Determined by 400 MHz ^{1}H NMR.



Interestingly, this study demonstrated that the

Table 2 summarizes the examination of the scope of this metal-catalyzed allylic alkylation reaction, under the optimized reaction conditions (Table 1, entry 6), in which a predictive model is evident for the optimum nucleophile/electrophile combination (eq 2, E = CO_2Me).

(1) Gawley, R. E.; Aubé, J. In *Principles of Asymmetric Synthesis*; Baldwin, J. E., Magnus, P. D., Eds.; Pergamon: New York, 1996; Vol. 14.

(2) Tsuji, J. In *Palladium Reagents and Catalysts*; Wiley: New York, 1996; Chapter 4, pp 290−404. For a recent review on the transition metal-catalyzed allylic alkylation, see: Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.

(3) For examples of allylic alkylation with branched malonates, see: (a) W: Trost, B. M.; Hung, M.-H. *J. Am. Chem. Soc.* **1983**, *105*, 7757. (b) Mo: Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104. (c) Ir: Takeuchi, R.; Tanabe, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 1975 and references therein.

(4) For an enantiospecific palladium-catalyzed allylic alkylation, see: Ziegler, F. E.; Cain, W. T.; Kneisley, A.; Stirchak, E. P.; Wester, R. T. *J. Am. Chem. Soc.* **1988**, *110*, 5442.

(5) Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581.

(6) (a) Evans, P. A.; Nelson, J. D. *Tetrahedron Lett.* **1998**, *38*, 1725. (b) Evans, P. A.; Robinson, J. E.; Nelson, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 6761. (c) Evans, P. A.; Robinson, J. E. *Org. Lett.* **1999**, *1*, 1929. (d) Evans, P. A.; Leahy, D. K. *J. Am. Chem. Soc.* **2000**, *122*, 5012. (e) Evans, P. A.; Kennedy, L. J. *Org. Lett.* **2000**, *2*, 2213.

(7) For other rhodium-catalyzed allylic alkylation reactions, see: (a) Minami, I.; Shimizu, I.; Tsuji, J. *J. Organomet. Chem.* **1985**, *296*, 269. (b) Takeuchi, R.; Kitamura, N. *New J. Chem.* **1998**, 659. (c) Fagnou, K.; Lautens, M. *Org. Lett.* **2000**, *2*, 2319 and references therein.

(8) (a) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313. (b) Shreeve, J. M.; Williamson, S. M. *Organometallics* **1984**, *3*, 1104.

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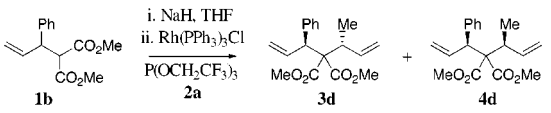
Table 3. Probing Nucleophile/Electrophile Stereochemical Implications on Selectivity



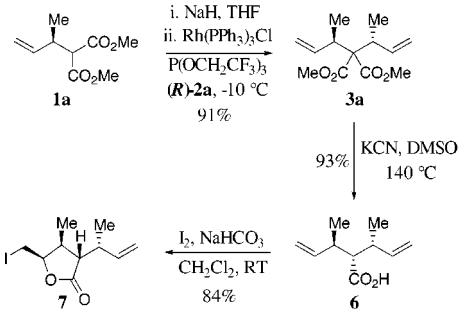
entry	malonate **1b**[a]	carbonate (**2a**)	2°:1° (**3d**+**4d**):**5d**[b]	ds **3d**:**4d**[b]	% ee of **3d**[c]	yield (%)[d]
1	(*R*)-	(*R*)-	35:1	30:1	≥90	91
2	(*R*)-	(*S*)-	8:1	2:1	60[11]	72
3	(*R*)-	(*RS*)-	17:1	6:1	≥90	89
4	(*RS*)-	(*RS*)-	27:1	18:1	0	87
5	(*RS*)-	(*R*)-	30:1	19:1	60	88[e]

[a] All reactions were carried out on a 0.2 mmol reaction scale at 30 °C with 1.5 equiv of **1b**. [b] Ratios of regio- and diastereoisomers were determined by capillary GLC. [c] Enantiomeric excess was determined by 400 MHz ^{1}H NMR using the shift reagent (+)-Eu(tfc)$_3$. [d] Isolated yields. [e] The alkylation reaction was carried out with 3 equiv of **1b**.

relative size of the α*-branched malonate has a marginal influence on regioselectivity (entries 1, 4, and 7), whereas the nature of the secondary allylic carbonate imparts significant control on this parameter (entries 1*−*3).* For example, the allylic alkylation with phenyl and benzyloxymethyl allylic carbonates **2b** (97% ee) and **2c** (≥99% ee) leads to diminished (entries 2, 5, and 8) and complete reversal in regioselectivity, respectively (entries 3, 6, and 9). The ability to completely alter the mode of alkylation in the latter example was attributed to the proximal ligation of the benzyloxymethyl substituent with the more electrophilic metal−allyl intermediate, which is presumably a function of the increased π-acidity of the fluorophosphites.[10] Nonetheless, this provides a synthetically useful method for the construction of (*E*)-primary allylic ethers. The diastereospecificity follows a similar trend to the regioselectivity, albeit with the exception of **1b** (Entries 4 and 5). Overall, this investigation provides a predictive model for achieving the optimum selectivity in a specific cross-coupling reaction (*i.e.*, entry 2 *vs* 4; in which **3b** = **3d** for this study).

The diastereospecificity obtained with (*R*)-**2a** (Table 3, entry 1) prompted the examination of the enantiomeric carbonate (*S*)-**2a** (96% ee), which was expected to furnish the *syn*-isomer **4d**, and thus establish whether the reaction has a mismatched component.[9] Surprisingly, the allylic alkylation of (*S*)-**2a** with (*R*)-**1b** furnished the *anti*-diastereoisomer **3d**, albeit with diminished selectivity (entry 2).[11] The ability to reverse the selectivity in this manner prompted the examination of the racemic carbonate (*RS*)-**2a**, which was anticipated to facilitate a more diastereoselective alkylation. Treatment of the allylic carbonate (*RS*)-**2a** with (*R*)-**1b** under the standard reaction conditions furnished **3d**/**4d** with improved diastereoselectivity favoring **3d** (entry 3). Hence, given the propensity for the alkylation to favor the formation of the *anti*-diastereoisomer, irrespective of absolute configuration, a competition experiment was devised to determine the degree of diastereoselectivity *vs* diastereospecificity. Treatment of the allylic carbonate (*RS*)-**2a** with the sodium salt of (*RS*)-**1b** under standard reaction conditions furnished *rac*-**3d** with excellent selectivity consistent with a diastereospecific transformation (entry 4). Therefore, an additional experiment was required to determine the degree of racemization of the metal−allyl intermediate. Treatment of the allylic carbonate (*R*)-**2a** (95% ee) with the sodium salt of the racemic α-branched malonate (*RS*)-**1b** furnished the 1,3-alkylation adducts **3d**/**4d**, favoring **3d** albeit with reduced enantiomeric excess (entry 5). Hence, the erosion of enantiospecificity is consistent with a more fluxional organorhodium intermediate, which is contrary to our earlier investigations.[5]

Scheme 1



C_2-symmetrical fragments provide versatile synthons for the construction of complex stereochemical arrays (vide supra). We envisioned that the desymmetrization of C_2-symmetrical 1,3-carbon stereogenic centers would provide an expeditious route to stereotetrads.[1] Initial studies focused on improving the selectivity in the formation of **3a** by lowering the reaction temperature. Treatment of the secondary carbonate (*R*)-**2a** (95% ee) with the sodium salt of **1a** (93% ee) under the rhodium-catalyzed allylic alkylation reaction conditions at −10 °C furnished the alkylation product **3a** in 91% yield, with improved selectivity (*2°:1°* = 24:1; *ds* = 26:1; *cf*. Table 1, entry 6). Krapcho decarboxylation/saponification of the diester **3a** furnished the *pseudo*-C_2-symmetrical carboxylic acid **6**, which was then desymmetrized with iodine to furnish the iodolactone **7** in 84% yield (*ds* ≥ 30:1).[12,13]

In conclusion, we have developed a new allylic linchpin cross-coupling reaction for the construction of *anti*- and *C$_2$-symmetrical* 1,3-carbon stereogenic centers through sequential enantiospecific and regioselective rhodium-catalyzed allylic substitution reactions. This study provided evidence for a more fluxional organorhodium intermediate, which is clearly matched for the formation of the *anti*-diastereoisomer, while somewhat mismatched for the alternative diastereoisomer. Finally, this approach provides an expeditious route to *pseudo*-C_2-symmetrical fragments that can be desymmetrized into important synthons for target-directed synthesis.

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Supporting Information Available: Representative experimental procedures and spectral data for **3a**−**i**, **6**, and **7** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The alkylation of (*R*)-**1a** with (*S*)-**2a** furnished the *meso*-product **4** in 86% yield, as the major diastereoisomer (ds = 4:1; 2°:1° = 12:1).

(10) For an excellent review on substrate-directable chemical reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(11) The erosion of the enantiomeric excess for the mismatched alkylation, while unclear, may be attributed to the epimerization of **4d** at the benzylic position which would result in the enantiomer of **3d**.

(12) (a) Krapcho, A. P. *Synthesis* **1982**, 805. (b) Kurth, M. J.; Brown, E. G.; Lewis, E. J.; McKew, J. C. *Tetrahedron Lett.* **1988**, *29*, 1517.

(13) For the iodolactone desymmetrization of the racemic *pseudo*-C_2-symmetrical carboxylic acid, see: Kurth, M. J.; Brown, E. G. *J. Am. Chem. Soc.* **1987**, *109*, 6844.