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Diastereoselective Palladium-Catalyzed α-Arylation of 4-Substituted Cyclohexyl Esters

Eric A. Bercot,* Seb Caille,* Tracy M. Bostick, Krishnakumar Ranganathan, Randy Jensen, and Margaret M. Faul

Chemical Process R&D, Amgen Inc., One Amgen Center Drive, Thousand Oaks, California 91320

ebercot@amgen.com; scaille@amgen.com

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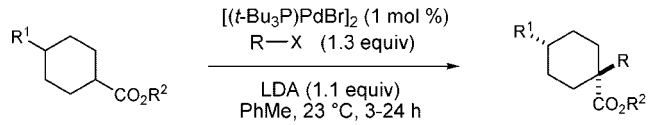
ABSTRACT



17 Examples
37-85 % yield
up to 37 : 1 dr

A diastereoselective palladium-catalyzed arylation of 4-substituted cyclohexyl esters has been developed. The reaction proceeds at room temperature in the presence of [(*t*-Bu$_3$P)PdBr]$_2$ providing products in up to 37:1 dr.

Target molecules containing quaternary carbon centers are particularly challenging to assemble, and methods to access these substrates continue to be an area of intense investigation.[1] The reaction of α,α-disubstituted enolates with a carbon-based electrophiles provides direct, efficient, and selective access to carbonyl compounds possessing fully substituted α-carbons.[2] Palladium-catalyzed vinylation[3] and arylation[4] of carbonyl compounds has emerged as a particularly powerful method to access carbonyl compounds bearing C(sp^2)-hybridized subustituents at the α-position.[5]

During the course of a recent research program, we required a concise and selective method to access 4-substituted cyclohexyl aryl ester **1**. Although 1,4 disubstituted cyclohexane derivatives are achiral due to the presence of a C_2-symmetry element, the selective preparation of either of the two possible achiral diastereomers represents a significant synthetic challenge.[6]

We envisioned accessing the desired ester **1** via a diastereoselective Pd-catalyzed arylation of 4-substituted cyclohexyl ester **2** (Scheme 1).[7,8] Oxidative addition of a low-valent palladium catalyst to aryl halide **3** followed by ligand substitution by

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(3) (a) Piers, E.; Marais, P. C. *J. Org. Chem.* **1990**, *55*, 3454–3455. (b) Chieffi, A.; Kamikawa, K.; Ahman, J.; Fox, J. M.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1897–1900. (c) Huang, J.; Bunel, E.; Faul, M. M. *Org. Lett.* **2007**, *9*, 4343–4346.

(4) For seminal examples of ketone arylation, see: (a) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108–11109. (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382–12383. (c) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 1740–1742.

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(6) For stereoselective approaches to a similar 4-substituted cyclohexane core, see: (a) Scott, J. P.; Lieberman, D. R.; Beureux, O. M.; Brands, K. M. J.; Davies, A. J.; Gibson, A. W.; Hammond, D. C.; McWilliams, C. J.; Stewart, G. W.; Wilson, R. D.; Dolling, U.-H. *J. Org. Chem.* **2007**, *72*, 4149–4155. (b) Davies, A. J.; Scott, J. P.; Bishop, B. C.; Brands, K. M. J.; Brewer, S. E.; DeSilva, J. O.; Dormer, P. G.; Dolling, U.-H.; Gibb, A. D.; Hammond, D. C.; Lieberman, D. R.; Palucki, M.; Payack, J. F. *J. Org. Chem.* **2007**, *72*, 4864–4871.

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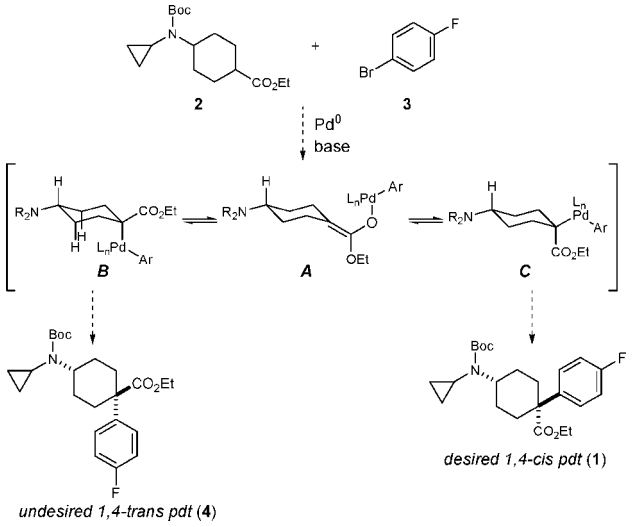
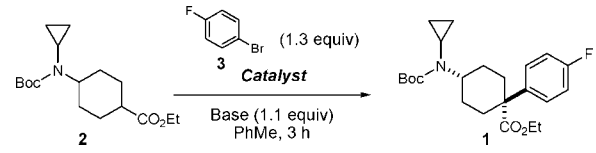
Scheme 1. Proposed Diastereoselective α-Arylation



the enolate derived from **2** would result in the formation of three interconverting Pd-enolates, O-bound complex **A** and C-bound complexes **B** and **C**.[9] Reductive elimination of **B** and **C** leads to undesired *trans*-ester **4** and desired *cis*-ester **1**, respectively.[10] We reasoned that the substituent at the 4-position should reside in the equatorial position[11] in intermediates **B** and **C**, thereby controlling the stereochemical course of the reaction.[12] Furthermore, the reaction should proceed via complex **C** due to the equatorial disposition of the group at the 4-position of the cyclohexyl ring and the sterically demanding arylpalladium substituent leading to desired ester **1**.[13]If the proposed reaction pathway is operative, not only should the reaction favor *cis*-ester products, but reaction selectivity should be a function of the steric profile (*A* value) of the ring substituent. Herein, we report that a variety of 4-substituted cyclohexyl ester derivatives undergo smooth α-arylation in the presence of a commercially available catalyst at room temperature providing the product aryl esters in moderate to excellent diastereoselectivity.

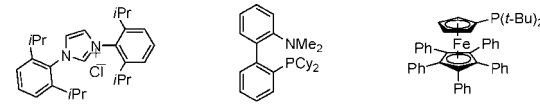
The coupling of aminocyclohexyl ester **2**[14] and *p*-fluorobromobenzene (**3**) was examined under several different conditions (Table 1). To our gratification, treatment of ester **2** with $LiNCy_2$ in toluene followed by exposure to aryl bromide **3** in the presence of 2.5 mol % of [(*t*-Bu_3P)$PdBr]_2$[15,16] at elevated temperatures provided the desired product in 78% yield and 19:1 dr, favoring the desired diastereomer **1**. Further optimization revealed that the reaction reaches completion at ambient temperature in less than 3 h; furthermore, catalyst loading was reduced to 1 mol % (entries 2 and 3). Although $LiNCy_2$ was an effective base, its use complicated the reaction workup due to the formation of insoluble amine salts. The use of LDA as base proved effective and alleviated workup problems providing the desired product **1** in 73% isolated yield and 32:1 dr (entry

Table 1. Reaction Optimization



entry[a]	catalyst[b] (mol %)	base	*T* (°C)	yield[c] (%)	dr[e]
1	[(*t*-Bu_3P)$PdBr]_2$ (2.5)	$LiNCy_2$	80	78	19:1
2	[(*t*-Bu_3P)$PdBr]_2$ (2.5)	$LiNCy_2$	23	92	ND
3	[(*t*-Bu_3P)$PdBr]_2$ (1.0)	$LiNCy_2$	23	77	ND
4	[(*t*-Bu_3P)$PdBr]_2$ (1.0)	LDA	23	83 (73)	32:1
5	$Pd_2(dba)_3$/*t*-Bu_3P (1.0)	LDA	23	37[d]	32:1
6	$Pd_2(dba)_3$/**5** (1.0)	LDA	23	14[d]	24:1
7	$Pd_2(dba)_3$/**6** (1.0)	LDA	23	76[d]	99:1
8	$Pd_2(dba)_3$/**7** (1.0)	LDA	23	66[d]	99:1

[a] Ester **2** was treated with 1.1 equiv of base at 0 °C for 15 min followed by addition of catalyst and 1.3 equiv of aryl bromide **3** and warming to indicated temperature for 3 h. [b] Ligand/Pd ratio 1:1. [c] HPLC assay yield, isolated yields in parentheses. [d] Reaction run for 24 h at ambient temperature. [e] Diastereomeric ratios determined by ^{19}F NMR of crude reaction mixtures.



(7) The Pd-catalyzed arylation of 4-methylcyclohexyl esters has been reported but no selecitvity data was provided; see: John, V.; Maillard, M.; Tucker, J.; Jagodzinske, B.; Brogley, L.; Tung, J.; Shah, N.; Neitz, J. R. **2005**, WO 05087752.

(8) For selected examples of diastereoselective intramolecular Pd-catalyzed α-arylation reactions, see: (a) Reisman, S. E.; Ready, J. M.; Weiss, M. M.; Hasuoka, A.; Hirata, M.; Tamaki, K.; Ovaska, T. V.; Smith, C. J.; Wood, J. L. *J. Am. Chem. Soc.* **2008**, *130*, 2087–2100. (b) MacKay, J. A.; Bishop, R. L.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 3421–3424. (c) Sole, D.; Vallverdu, L.; Solans, X.; Font-Bardia, M.; Bonjoch, J. *J. Am. Chem. Soc.* **2003**, *125*, 1587–1594. (d) Muratake, H.; Nakai, H. *Tetrahedron Lett.* **1999**, *40*, 2355–2358. (e) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7581–7582. For selected examples of diastereoselective intermolecular α-aryaltion reactions, see: (f) Iwama, T.; Rawal, V. H. *Org. Lett.* **2006**, *8*, 5725–5728. (g) Konopelski, J. P.; Lin, J.; Wenzel, P. J.; Deng, H.; Elliot, G. I.; Gerstenberger, B. S. *Org. Lett.* **2002**, *4*, 4121–4124. (h) Elliott, G. I.; Konopelski, J. P.; Olmstead, M. M. *Org. Lett.* **1999**, *1*, 1867–1870.

(9) (a) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 5816–5817. (b) Culkin, D. A.; Hartwig, J. F. *Organometallics* **2004**, *23*, 3398–3416.

(10) The *trans* and *cis* descriptor refer to the relationship between the carbonyl functional group present on the fully substituted carbon atom and the substituent at the 4-position.

(11) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley and Sons: New York, 1994; pp 686−771.

(12) For the diastereoselective alkylation of 4-substituted cyclohexyl carbonyl derivatives, see: (a) House, H. O.; Bare, T. M. *J. Org. Chem.* **1968**, *33*, 934–949. (b) Ziegler, F. E.; Wender, P. A. *J. Org. Chem.* **1977**, *42*, 2001–2002. (c) Krapcho, A. P.; Dundulis, E. A. *J. Org. Chem.* **1980**, *45*, 3236–3245.

(13) We postulated that not only should the equilibrium favor complex **C**, but reductive elimination from **C** to **1** should proceed via a lower energy transition state versus the reductive elimination of **B** to **4**.

(14) Cyclohexyl ester **2** was accessed in two steps from commercially available materials and used as a 2:1 mixture of isomers.

(15) Commercially available from Johnson Matthey (CAS no. 185812-86-6; catalog no. Pd-113).

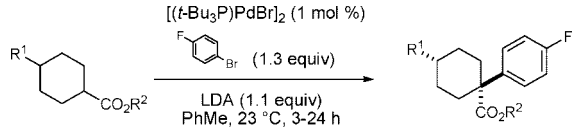
(16) For recent reports detailing the use of this catalyst, see: (a) Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 4746–4748. (b) Hama, T.; Liu, X.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 11176–11177. (c) Hama, T.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 1545–1548. (d) Hama, T.; Hartwig, J. L. *Org. Lett.* **2008**, *10*, 1549–1552.

4). The catalyst derived from mixing $Pd_2(dba)_3$ and *t*-Bu_3P in a 1:1 ratio proved much less effective (entry 5). Additional ligand−Pd complexes were examined under optimized conditions. Imidazolium-based ligand **5**[17] provided material in high selectivity, but the yield was low (entry 6). Phosphines **6**[18] and **7**[19] provided highly enriched product **1**. However, these reactions failed to reach complete conversion after 24 h at ambient temperature (entries 7 and 8).

With the identification of effective conditions for the diastereoselective arylation of ester **2**, we sought to expand the substrate scope of the present transformation. A variety of 4-substituted cyclohexyl esters undergo diastereoselective arylation (Table 2). Cyclohexyl esters bearing the sterically demanding *tert*-butyl (**8**) and trifluoromethyl (**10**)[20] groups at the 4-position provide arylated products in 13.0:1 and 10.5:1 dr, respectively (entries 1 and 2). Methyl-substituted ethyl ester **12** smoothly undergoes arylation providing **13** in 5.3:1 dr and 77% isolated yield (entry 3). The identity of the ester plays and important role in the reaction. Methyl ester **14** provides the product **15** in a slightly higher diastereomeric ratio than the corresponding ethyl ester **12**, while *tert*-butyl ester **16** provides a marked increase in selectivity providing **17** in 10.0:1 dr and 85% yield (entries 4 and 5). The diastereoselective arylation is not limited to 4-substituted cyclohexyl esters with 3-methyl cyclohexyl ethyl ester **18** providing the product **19**[21] in good selectivity and yield (entry 6). Oxygen substitutents at the 4-position of the ring are well tolerated in the reaction providing products in good yield; however, reaction selectivity is low presumably due to the smaller steric profile of ether substituents (entries 7 and 8).[22] Substrates containing basic amines, exemplified by **24**, are competent in the reaction providing **25** in 4.0:1 dr and 81% isolated yield (entry 9). Intrigued by the high selectivity observed for ester **2**, we examined the corresponding methyl carbamate (**26**) and dimethyl urea (**28**) derivatives. Methyl carbamate **26** provided arylated product **27** in 37:1 dr while urea **29** provided product in a diminished 6.5:1 dr (entries 10 and 11). These results suggest that the high selectivity observed for substrates **2** and **26** (even higher than the *t*-Bu substituted ester **8**) are in part a result of the carbamate resident on the amine substituent and not the nature of the alkyl group present on the carbamate.

Having established a range of nucleophilic coupling partners capable of participating in the diastereoselective arylation reaction, we next explored the electrophile scope

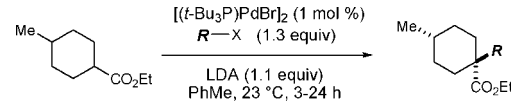
Table 2. Ester Scope of Diastereoselective Arylation Reaction



Entry[a]	Substrate[b]	Product	dr[c]	Yield (%)[d]
1	R = *t*-Bu (**8**)	R = *t*-Bu (**9**)	13.0 : 1	65
2	R = CF_3 (**10**)	R = CF_3 (**11**)	10.5 : 1	78
3	R = Me (**12**)	R = Me (**13**)	5.3 : 1	77
4	R = Me (**14**)	R = Me (**15**)	8.2 : 1	74
5	R = *t*-Bu (**16**)	R = *t*-Bu (**17**)	10.0 : 1	85
6	**18**	**19**	7.4 : 1	72
7	R = Me (**20**)	R = Me (**21**)	3.1 : 1	79
8	R = Bn (**22**)	R = Bn (**23**)	1.6 : 1	43[e]
9	**24**	**25**	4.0 : 1	81
10	R = COOMe (**26**)	R = COOMe (**27**)	37 : 1	45
11	R = $CONMe_2$ (**28**)	R = $CONMe_2$ (**29**)	6.5 : 1	71

[a] Ester was treated with 1.1 equiv of LDA at 0 °C for 15 min followed by addition of catalyst and 1.3 equiv of aryl bromide and warming to ambient temperature. [b] Used as a mixture of cis,trans isomers. [c] Diastereomeric ratios and relative stereochemistry determined by NMR. [d] Isolated yield. [e] Isolated yield of major diastereomer.

Table 3. Electrophile Scope



Entry[a]	Electrophile[b]	Product	dr[c]	Yield (%)[d]
1	X = Br (**30**)	**31**	8.6 : 1	78
2	X = OTf (**32**)		--	NR
3	X = Cl (**33**)		--	< 10
4	**34**	**35**	2.7 : 1	37[e,f]
5	**36**	**37**	7.9 : 1	78
6	**38**	**39**	4.5 : 1	84
7	**40**	**41**	10.3 : 1	78

[a] Ester was treated with 1.1 equiv of LDA at 0 °C for 15 min followed by addition of catalyst and 1.3 equiv of electrophile and warming to ambient temperature. [b] Used as a mixture of cis,trans isomers. [c] Diastereomeric ratios and relative stereochemistry determined by NMR. [d] Isolated yield. [e] Reaction carried out at 80 °C. [f] Isolated yield of 9.2:1 mixture ofdiastereomers.

(Table 3). Bromo toluene **30** smoothly provided the desired arylation product **31** in 8.6:1 dr (entry 1). The use of the corresponding aryl triflate and chloride resulted in little to no product formation even at elevated temperatures and prolonged reaction times (entries 2 and 3). The efficiency and selectivity of the reaction is sensitive to sterics as exemplified by the coupling reaction of 2-bromo toluene (**34**) which required high reaction temperatures and provided arylated product **35** in modest selectivity and yield (entry 4). Both electron-rich and electron-deficient 4-substitued aryl bromides efficiently couple providing **37** and **39** in good yield (entries 5 and 6). It is interesting to note that the electronic nature of the coupling partner has an impact on reaction selectivity with electron rich aromatics providing products in higher diastereomeric ratios. Vinyl bromides are competent coupling partners with 2-bromopropene (**40**) providing product **41** in 10.3:1 dr and 78% isolated yield (entry 7).

In conclusion, we have identified a palladium-catalyzed diatasteroselective arylation of 4-substituted cyclohexylesters that provides the product esters, bearing an α-quaternary carbon center, in good yield and selectivity. The reaction proceeds at room temperature in the presence of 1 mol % of a commercially available catalyst providing the product of equatorial approach of the electrophile as the major diastereomer in all cases examined. Diastereoselectivity in the present reaction generally increases with the *A* value of the substituent present at the 4-position of ring; furthermore, increasing the steric demand of the ester leads to increased selectivity. Additionally, we have observed that the stereochemical course of the reaction is also influenced by the nature of the electrophilic coupling partner.

Acknowledgment. We thank Dr. Tiffany Correll and Dr. Kevin Turney for their assistance with DSC and HRMS measurements. We also thank Dr. Jay Powers and Dr. Lisa Julian for helpful discussions.

Supporting Information Available: General procedures and spectra for obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) The $-CF_3$ group is estimated to be isosteric with $-i$-Pr; see: Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *101*, 6119–6146, and references therein.

(21) The major diastereomer is the product resulting from the reductive elimination of an intermediate in which the palladium and methyl substituents are both disposed in equatorial positions in analogy to the arylated products obtained in the 4-substituted series.

(22) Selected *A* values (kcal mol^{-1}) for substituents in cyclohexane ring systems (see ref 11): $-Me = 1.74$; $-t$-Bu $= 4.7-4.9$; $-CF_3 = 2.4-2.5$; $-OMe = 0.55-0.75$.