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A Diastereoselective Intermolecular Heck Reaction of 1,3-Dioxepins

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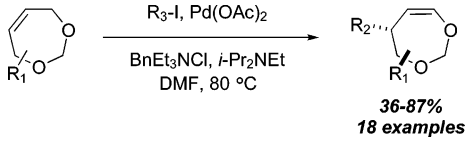
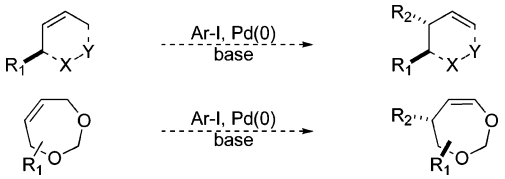
ABSTRACT



A highly diastereoselective intermolecular Heck reaction of 1,3-dioxepins is reported. Substitution at both the 2- and 4-positions of the dioxepin directs the Pd coordination and subsequent olefin insertion to provide the *trans*-disubstituted adduct in good yield and high diastereoselectivity. Chemoselective Heck reaction occurs at the dioxepin alkene in the presence of other olefinic functional groups. A labeling study has been conducted which suggests that the reaction is under kinetic control.

The intramolecular Heck reaction has been extensively investigated and has played a crucial role in the successful synthesis of complex molecules.[1,2] In stark contrast stands the current state-of-the-art in the intermolecular Heck reaction when using acceptors other than acyclic olefins. Perhaps most illustrative of this issue is that only the simplest cyclic olefins participate well in the asymmetric intermolecular Heck reaction.[3] A significant exception to this statement lies in the asymmetric Heck reaction of dioxepins developed independently by Shibasaki and Pfaltz.[4,5] Only recently has the diastereoselective intermolecular Heck reaction been explored, where diastereoselectivity is induced by chelation of an auxiliary.[6,7] In the absence of the directing influence of an auxiliary, the reaction should proceed through a pair of competing transition states where the level of diastereoselection is dictated by sterics alone (Scheme 1).

Scheme 1



There are few examples of this type of diastereoselective Heck reaction. Larock and co-workers illustrated a diastereoselective Heck reaction that provides *trans*-2,5-diaryltetrahydrofurans en route to platelet-activating factor antagonists.[8] Takano has shown that a Heck reaction of a vinyl halide on a 2-aryl-substituted dioxepin proceeds with high diastereoselectivity en route to asarinin.[9] More recently,

(1) See, for example: (a) Morphine: Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 11028−11029. (b) Gelsemine: Madin, A.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 18054−18065.

(2) For some excellent reviews of the Heck reaction, see: (a) Daves, G. D., Jr.; Hallberg, A. *Chem. Rev.* **1989**, *89*, 1433−1445. (b) Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379−2411. (c) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314−321. (d) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066. (e) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945−2963.

(3) (a) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417−1419. (b) Shibasaki, M.; Vogl, E. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 1, p 457.

(4) (a) Koga, Y.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1994**, *35*, 1227−1230. (b) Loiseleur, O.; Meier, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 200−202.

(5) For a recent report of an asymmetric intermolecular oxidative Heck-type reaction, see: Yoo, K. S.; Park, C. P.; Yoon, C. H.; Sakaguchi, S.; O'Neill, J.; Jung, K. W. *Org. Lett.* **2007**, *9*, 3933−3935.

(6) (a) Buezo, N. D.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **1998**, *120*, 7129−7130. (b) de la Rosa, J. C.; Diaz, N.; Carretero, J. C. *Tetrahedron Lett.* **2000**, *41*, 4107−4111. (c) Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2003**, *125*, 3430−3431.

(7) For a microreview on neighboring-group effects in the Heck reaction, see: Oestreich, M. *Eur. J. Org. Chem.* **2005**, 783−792.

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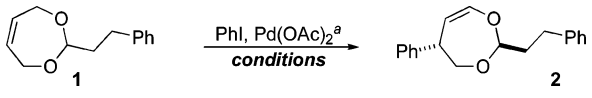
Correia and co-workers described a diastereoselective Heck reaction of substituted pyrrolines with arenediazonium salts as an approach to aryl kainoids.[10]

We became interested in a diastereoselective Heck reaction of 1,3-dioxepins as a route to polysubstituted substrates which would undergo stereoselective [1,3]-rearrangements to afford tetrahydrofurans, an approach that we have already documented.[11] In order to maximize efficiency, we required the reaction to use equimolar amounts of the aryl halide and olefin, a condition not commonly found in asymmetric intermolecular Heck reactions.[12] Herein we report the scope of the diastereoselective intermolecular Heck reaction using 1,3-dioxepins as substrates.

Initial experiments revealed that the diastereoselectivity is dependent on concentration (entries 1 and 2, Table 1).

Table 1. Reaction Optimization



entry	conditions	dr (*trans*:*cis*)
1	PPh_3, K_2CO_3, *n*-Bu_4NCl 0.1 M MeCN/H_2O (9:1), 50 °C	**33:67**
2	PPh_3, K_2CO_3, *n*-Bu_4NCl 1 M MeCN/H_2O (9:1), 50 °C	**85:15**
3	1 equiv *i*-Pr_2NEt, $BnEt_3NCl$ DMF, 80 °C	**95:5**
4	3 equiv *i*-Pr_2NEt, $BnEt_3NCl$ DMF, 80 °C	>**95:5**[b]

[a] Reactions were preformed with 5−8 mol % of $Pd(OAc)_2$. [b] The minor diastereomer was not observed by ^1H NMR.

We hypothesized that a more organic-soluble base would serve to increase the rate of X−Pd−H decomposition, thus suppressing the undesired Pd−H-mediated epimerization of the desired *trans*-diastereomer. The reaction, when conducted using our optimized modified Jeffery conditions,[13,14] provides the desired dioxepin in excellent yield and selectivity (entry 3). The concentration of base also plays a role under the optimized conditions, although the effect is not as pronounced (95:5 vs >95:5, entries 3 and 4). It is worthy of note that, in both of the described Heck conditions, an induction period of 10 min is critical in obtaining a solution that contains active catalyst, during which there is a color change from orange to red-brown.[15,16]

The halide scope of the reaction was evaluated. Iodobenzene is a competent coupling partner, while the reaction is sluggish when bromobenzene is used (85% vs 32% after 24 h). Phenyl triflate does not participate under these conditions.

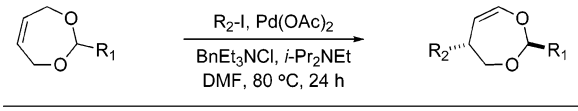
The scope of the desymmetrizing Heck reaction of 1,3-dioxepins with respect to substitution at the acetal position is broad. Simple alkyl, and electron-rich and -deficient aromatic substitution is well tolerated (entries 1, 2, 6, and 8, Table 2). The stereochemistry of the Heck adducts was determined to be *trans* by NOE experiments and single-crystal X-ray diffraction analysis of **8**. Pendant and strained cyclopropane and cyclobutane substituents remain intact under the reaction conditions (entries 3−5, 7, and 9). Chemoselectivity for the dioxepin olefin is exclusive in the presence of other potentially reactive *E*-olefins (entries 10 and 11). Unprotected alcohols are also tolerated and exhibit no deleterious effects on the reaction (entry 5). The coupling partner scope is also quite broad, where electron-rich aryl,[17] 1,2-disubstituted, 1,1-disubstituted, and trisubstituted[18] alkenyl iodides provide dioxepin products with good diastereoselectivity and respectable yields[19] (entries 6−9).

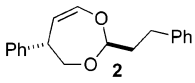
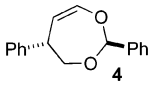
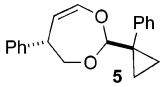
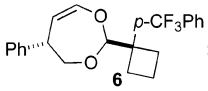
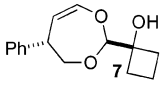
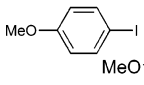
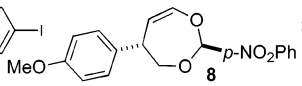
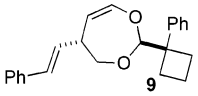
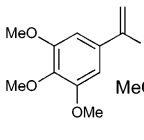
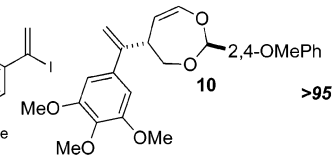
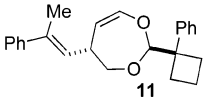
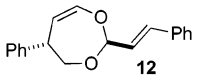
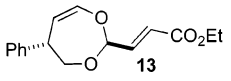
Dioxepins that contain a preexisting stereocenter at the 4-position are also competent olefins for the Heck reaction (Table 3). Electron-rich, -neutral, and -deficient aromatics all couple in excellent diastereoselectivity and good yield to provide the *trans*-dioxepin products (entries 1−3). Interestingly, when the size of the substituent at the dioxepin 4-position reaches a steric threshold, the reverse olefin insertion becomes competitive (entries 5 and 6) and in the extreme is the major product (entry 7).

In order to rationalize the stereochemistry of the products, we considered thermodynamic versus kinetic selectivity. It has been established that alkenes can "walk" under a variety of Heck conditions by Pd−H-mediated isomerization to the more thermodynamically favored position.[20] To evaluate this possibility, 3,3,6,6-$^2H_4$-dioxepin **23** was synthesized. If the *trans*-dioxepin is produced by thermodynamic selectivity (isomerization/epimerization by Pd−H or Pd−D), there should be ^2H enrichment at the 5-position and ^1H enrichment at the 7-position of the dioxepin. If kinetic selectivity predominates, then no 5-^2H or 7-^1H enrichment should be observed. Exposure of **23** to the optimized modified Jeffery

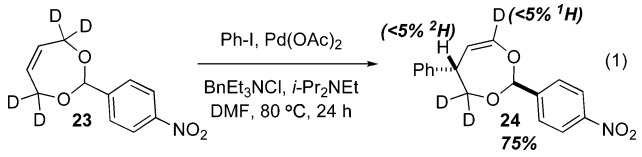
(8) Larock, R. C.; Gong, W. H. *J. Org. Chem.* **1990**, *55*, 407−408.
(9) Takano, S.; Samizu, K.; Ogasawara, K. *Synlett* **1993**, 785−787.
(10) da Silva, K. P.; Godoi, M. N.; Correia, C. R. D. *Org. Lett.* **2007**, *9*, 2815−2818.
(11) (a) Nasveschuk, C. G.; Jui, N. T.; Rovis, T. *Chem. Commun.* **2006**, *29*, 3119−3121. (b) Nasveschuk, C. G.; Rovis, T. *J. Org. Chem.* **2007**, in press.
(12) See ref 4.
(13) (a) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113−10130. For examples of modified Jeffery's conditions in the Heck reaction, see: (b) Reference 9. (c) Ogasawara also reported a singular example: Samizu, K.; Ogasawara, K. *Chem. Lett.* **1995**, 543−544. A useful resource for conditions commonly used in Heck reactions: (d) Heck, R. F. *Org. React.* **1982**, *27*, 345−390.
(14) We optimized these conditions to be as follows: 1.05 equiv of ArI, 1 equiv of dioxepin, 8 mol % of $Pd(OAc)_2$, 2 equiv of $BnEt_3NCl$, 3 equiv of *i*-Pr_2NEt, 0.4 M in DMF (with respect to the alkene) at 80 °C.
(15) This observation is consistent with the formation of Pd nanoparticles and/or colloids which have been implicated in the Heck reaction and other Pd-catalyzed reactions: (a) Consorti, C. S.; Zanini, M. L.; Leal, S.; Ebeling, G.; Dupont, J. *Org. Lett.* **2003**, *5*, 983−986. (b) de Vries, A. H. M.; Mulders, J. M. C. A.; Mommers, J. H. M.; Henderickx, H. J. W.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 3285−3288. (c) Consorti, C. S.; Flores, F. R.; Dupont, J. *J. Am. Chem. Soc.* **2005**, *127*, 12054−12065.
(16) For procedures and discussion about how to determine the "true" catalyst, see: (a) Lin, Y.; Finke, R. G. *Inorg. Chem.* **1994**, *33*, 4891−4910. (b) Widegren, J. A.; Finke, R. G. *J. Mol. Catal. A: Chem.* **2003**, *198*, 317−341. (c) Özkar, S.; Finke, R. G. *J. Am. Chem. Soc.* **2002**, *124*, 5796−5810.
(17) Electron-deficient aryl iodides, which undergo more facile oxidative addition, also participate; under unoptimized conditions (entry 2, Table 1), *p*-$CF_3C_6H_4I$ provides the dioxepin in 48% yield with 88:12 dr.
(18) Fourteen percent of another inseparable olefin isomer is produced.
(19) Vinyl iodide is invariably consumed; ∼20% unreacted dioxepin may be reisolated.
(20) See ref 2.

Table 2. Scope of Symmetric 1,3-Dioxepins



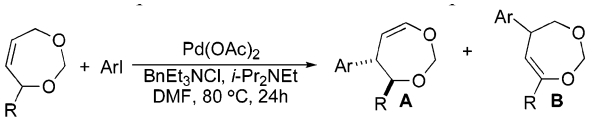
entry	R_2-I	product	dr	yield %
1		 **2**	*>95 : 5*	*87*
2		 **4**	*>95 : 5*	*85*
3		 **5**	*>95 : 5*	*80*
4		 **6**	*>95 : 5*	*80*
5		 **7**	*>95 : 5*	*72*
6		 **8**	*>95 : 5*	*67*
7		 **9**	*>95 : 5*	*50*
8		 **10**	*>95 : 5*	*45*
9		 **11**	*>95 : 5*	*36*
10		 **12**	*>95 : 5*	*77*
11		 **13**	*>95 : 5*	*64*

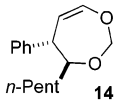
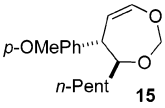
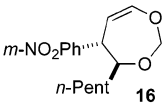
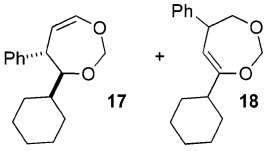
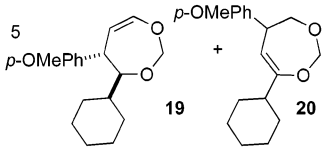
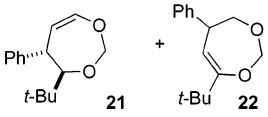
conditions showed no ^{2}H enrichment at the 5-position and no ^{1}H incorporation at the 7-position (eq 1).[21] When combined, these data suggest that the high levels of diastereoselection obtained under the optimized conditions are a result of *kinetic* selectivity and not epimerization by a long-lived Pd−H.



A potential rationale to explain the regioselectivity of Heck reactions on 4-substituted substrates may lie in a ground state

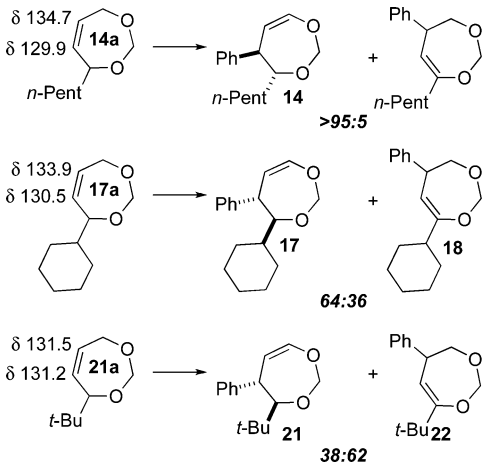
Table 3. Scope of 4-Substituted 1,3-Dioxepins



entry	products	product ratio (**A**:**B**)	yield %, (**A** dr)
1	 **14**	*>95:5*	*83, >95:5*
2	 **15**	*>95:5*	*81, >95:5*
3	 **16**	*>95:5*	*56, >95:5*
4	 **17** **18**	*64:36*	*84, >95:5*
5	 **19** **20**	*78:22*	*84, >95:5*
6	 **21** **22**	*38:62*	*61, >95:5*

differentiation of the dioxepin olefin carbons. A comparison of the ^{13}C chemical shifts of these atoms reveals that as steric bulk of the substituent is increased the parts per million difference decreases (**14a**, **17a**, **21a**, Scheme 2). This is presumably a reflection of a different ground state conformation of the dioxepin resulting from an increased steric demand

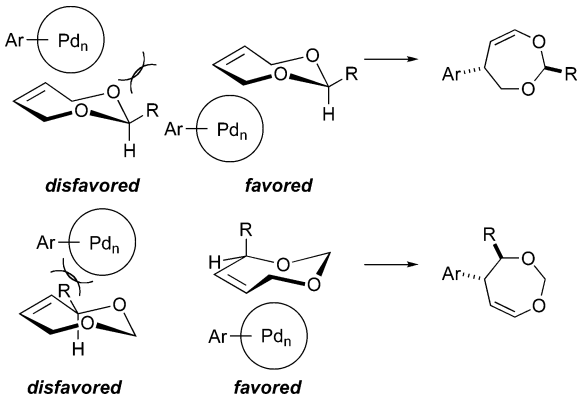
Scheme 2



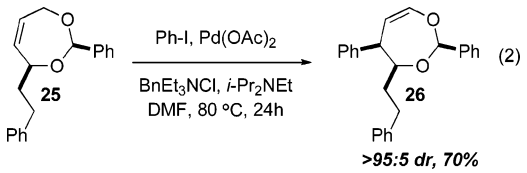
of the cyclohexyl and *tert*-butyl groups relative to *n*-pentyl. This difference may also manifest itself in an electronic manner, effectively polarizing the double bond. Whatever the underlying principle involved, this effect correlates well with the experimental results: as the steric bulk of the substituent is increased, regioselectivity decreases.

The relative stereochemistry may be rationalized by our proposed stereochemical model (Scheme 3). With 2-substituted dioxepins, coordination of the large Pd-alkyl species, whether a nanoparticle or monometallic-based, to the olefin occurs *trans* to the dioxepin substituent for steric reasons.[22] With 4-substituted dioxepins, olefin coordination *cis* to the allylic alkyl substituent is disfavored, a situation observed in many similar organometallic reactions involving allylically substituted olefins.[23]

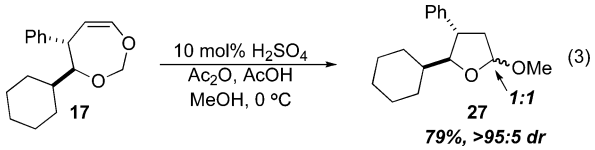
Scheme 3



We next directed our attention toward determining the combined effect of substitution at the 2- and 4-positions of the dioxepin. Surprisingly, we found that when *cis*-2,4-disubstituted dioxepin **25** was subjected to optimized conditions, the all *cis*-2,4,5-trisubstituted dioxepin was formed in good yield and excellent diastereoselectivity (eq 2).[24] This stereochemical outcome is not easily rationalized.



In related work, we have used the vinyl acetals obtained from these reactions in a stereoselective Lewis acid mediated ring contraction to form tri- and tetrasubstituted tetrahydrofurans.[11] We also note that simple acidic hydrolysis[4a] of compounds such as **17** leads to *trans*-disubstituted lactols and lactol ethers in good yield with preservation of stereochemistry (eq 3).



In summary, we have developed a general and highly *trans*-diastereoselective intermolecular Heck reaction of 1,3-dioxepins. Substitution at the 2- and 4-positions of 1,3-dioxepins leads to the *trans*-dioxepin product. Labeling studies suggest that the selectivity is kinetic in origin and not a result of an initial unselective olefin insertion followed by an epimerization event. The overall synthetic sequence provides an efficient and modular approach to the versatile 1,3-dioxepin framework.

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

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(21) Crossover experiments between **1** and **23**, and **1** and **24** using optimized modified Jeffery conditions also did not show any 2H enrichment at the 5-position and no 1H enrichment at the 7-position in the dioxepin product.

(22) Coordination of the Pd to the acetal oxygens is also a possibility; this type of interaction has been invoked to explain the stereochemical outcome of Fe-catalyzed [4 + 4] ene reactions of 1,3-dioxepins. See: Takacs, J. M.; Anderson, L. G.; Newsome, P. W. *J. Am. Chem. Soc.* **1987**, *109*, 2542−2544.

(23) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370.

(24) Relative stereochemistry was determined by NOE experiments. See Supporting Information for details.