Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 16 (2005) 3502–3505

Catalytic and stereoselective iodination of prochiral C–H bonds

Ramesh Giri, Xiao Chen, Xue-Shi Hao, Jiao-Jie Li, Jue Liang, Zi-Peng Fan and Jin-Quan Yu*

Department of Chemistry, Brandeis University, Waltham, MA 02454-9110, USA

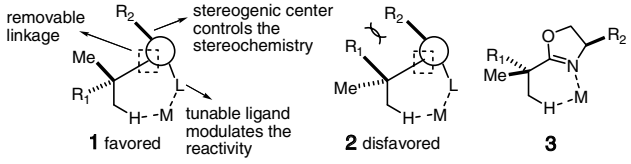
Received 1 August 2005; accepted 29 August 2005
Available online 10 November 2005

Abstract—Oxazolines were employed as cyclic chiral directing groups for stereoselective C–H activation. Oxazoline-directed cleavage of the β-C–H bonds followed by reaction with I_2 gave a wide range of iodinated products. A large range of functional groups are tolerated. PdI_2 was isolated in the reaction and found to be converted to $Pd(OAc)_2$ upon treatment with a combination of I_2 and $PhI(OAc)_2$ in situ to achieve catalytic turnover. Diastereoselective iodination of prochiral C–H bonds were also investigated.

1. Introduction

Various approaches have been employed in order to develop stereoselective C–H activation reactions.[1] Elegant syntheses of complex natural products have demonstrated the power of C–H activation reactions.[2] For example, an oxazoline Schiff base complex (Me_2PtL_2) was attached to a synthetic intermediate via an imine linkage to dehydrogenate a remote ethyl group stoichiometrically and diastereoselectively in the synthesis of (−)-rhazinilam.[2a] Recently, the well-established σ-chelation assisted stoichiometric C–H activation processes have emerged into an exciting research area focused on developing catalytic reactions.[3] Cyclometallation facilitated by pre-coordination to a σ-chelating group is one of the earliest observations of C–H activation.[4] Activation of aryl C–H bonds directed by an *ortho*-nitrogen chelating group to form dimeric cyclometallated complexes has been extensively reviewed.[5] Examples of cyclopalladation of aliphatic sp^3 C–H bonds to form the stable dimeric complexes have also been observed.[6] Interesting synthetic applications have been also achieved based on a stoichiometric oxime directed palladation, initially observed by Shaw in 1978.[7] The mechanism of cyclometallation reactions and application of palladacycles has been extensively reviewed.[8] Catalytic acetoxylation of C–H bonds using *O*-methyl oxime as a chelating group has been recently achieved.[9] However, further exploitation of this C–H activation pathway to stereoselectively functionalize sp^3 C–H bonds in commonly used starting materials remains a significant challenge.

From a viewpoint of synthetic utility, it is desirable to develop chiral directing groups that can be readily removed, after the C–H functionalization step, in order to produce broadly useful compounds. Therefore, we began to search for a combination of a removable chiral directing group and a metal center that would form reactive complexes and result in stereoselective C–H cleavage. It is well established that σ-chelation assisted C–H activation takes place through a cyclic transition state.[8] We, therefore, reasoned that the use of a cyclic chiral directing group could be advantageous in controlling the stereochemistry via a steric repulsion model (Scheme 1).



Scheme 1. Control of stereoselectivity in C–H activation.

2. Results and discussion

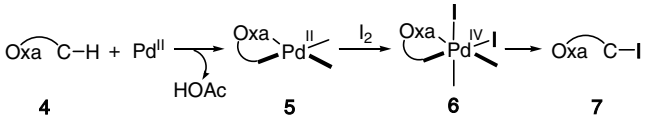
When R_1 is larger than the Me group, **1** is favored over **2** due to the less steric repulsion between Me and R_2 in **1**, thereby controlling the stereoselectivity in the C–H

* Corresponding author. Tel.: +1 781 736 5201; fax: +1 781 736 2516; e-mail: yu200@brandeis.edu

0957-4166/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2005.08.049

activation step. This hypothesis led us to focus on extensive exploration of a wide range of cyclic directing groups with the following criteria: (a) facile formation of either a three coordinate or square planar structure with a metal center that is known to be reactive for C–H cleavage,[10] and (b) readily available chiral analogues for diastereoselective C–H activation. Oxazolines, as shown in **3**, were initially selected to direct the activation of α-methyl groups in carboxylic acids. 2-Phenyloxazoline was previously observed to undergo *ortho*-C–H activation by $Pd(OAc)_2$ under reflux in HOAc to form the stable dimeric arylpalladium complex. A single case of stoichiometric activation of an α-methyl group in an oxazoline to form the five-membered dimeric palladocycle, was also observed.[6b] However, the formation of these stable dimeric Pd complexes has not been developed into a catalytic process to date.

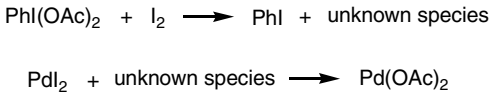
Based on previous work on the oxidative addition of I_2 onto Pt(II) or Pd(II) complexes coordinated to tridentate ligands,[11] we explored the following proposed reaction pathway to achieve diastereoselective iodination (Scheme 2). The preliminary results have recently been reported.[12] Herein, we report further investigations into functional group tolerance of the newly developed catalytic system, and the influence of the oxazoline structures on the reactivity and stereoselectivity.



Scheme 2. Proposed reaction pathway for iodination of unactivated C–H bonds.

Oxazolines were readily prepared from carboxylic acids and amino alcohols using a three-step sequence in one pot at room temperature.[13] In order to establish the C–H activation conditions, pivalic acid derived oxazoline **8** was initially tested. Stirring **8** (1 equiv) with $Pd(OAc)_2$ (1 equiv) and I_2 (1 equiv) in CH_2Cl_2 at 24 °C for 24 h exclusively led to the iodination of the methyl group to give mono-iodide **8a** in 80% isolated yield (Scheme 3). The quantitative formation of PdI_2 (characterized by powder X-ray diffraction) was also observed.

Since PdI_2 is not reactive, we screened various conditions to convert PdI_2 into $Pd(OAc)_2$ in order to achieve catalytic iodination reactions. Both $Ag(OAc)_2$ and $PhI(OAc)_2$[14] were found to be effective, the latter giving higher yields. It is worth noting that in the absence of I_2, the combination of $Pd(OAc)_2$ and $PhI(OAc)_2$ results in an acetoxylation reaction in a similar manner to a recently reported Pd-catalyzed acetoxylation reaction.[9] It should be pointed out that, unlike in the acetoxylation reaction, the role of $PhI(OAc)_2$ in this iodination reaction is not to oxidize Pd^{II} to Pd^{IV}. Instead, $PhI(OAc)_2$ reacts with I_2 to generate a new oxidant, which is responsible for converting PdI_2 into $Pd(OAc)_2$ (Scheme 4).

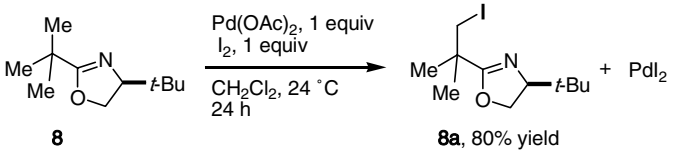


Scheme 4. Catalytic turnover.

Next, we tested the diastereoselective iodination using this catalytic protocol (for a typical procedure, see Ref. 15). We found that substituents on the 4-position of oxazolines have a dramatic impact on the reactivity and stereoselectivity. Iodination of oxazoline **9** derived from (*S*)-*tert*-leucinol gave the product **9a** in 92% yield and 25% de. Oxazoline **10** derived from (*S*)-valinol was less reactive under the same conditions and a complete loss of diastereoselectivity was observed. We also synthesized oxazolines **11**–**13** to test how the substituents at the 4-position affect the reactivity and diastereoselectivity. The iodination of **11**–**13** gave low yields of the iodinated products **11a**–**13a** with poor diastereoselectivity. Oxazolines **14**–**15** were prepared in order to further investigate how the reaction rate is influenced by the oxazoline structure. The absence of a substituent or the presence of a phenyl group at the 4-position was found to decrease the reaction rate. From these results, the presence of a bulky *tert*-butyl group at the 4-position is crucial for both the reactivity and stereoselectivity.

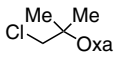
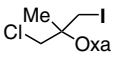
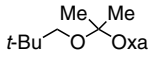
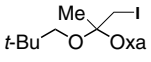
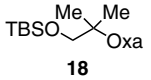
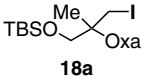
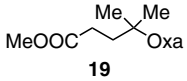
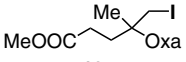
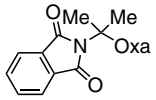
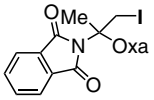
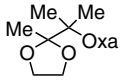
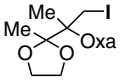
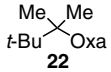
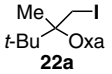
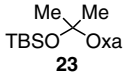
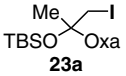
A variety of functional groups such as halides, esters, ethers, and imides were found to be compatible with this catalytic system (Table 1). We were pleased to find that the presence of a bulky group at the α-position of oxazolines drastically improved the diastereoselectivity (entries 7 and 8). This is consistent with the proposal that the steric repulsion between the α-substituent and the 4-substituent on the oxazoline controls the stereochemistry. The selective activation of methylene over methyl group in oxazoline **24**, although surprising, is consistent with the previously reported amide directed lithiation of a cyclopropyl group.[16]

The diastereoselective C–H activation of prochiral aryl C–H bonds was also achieved using substrate **25**. The



Scheme 3. Stoichiometric iodination.

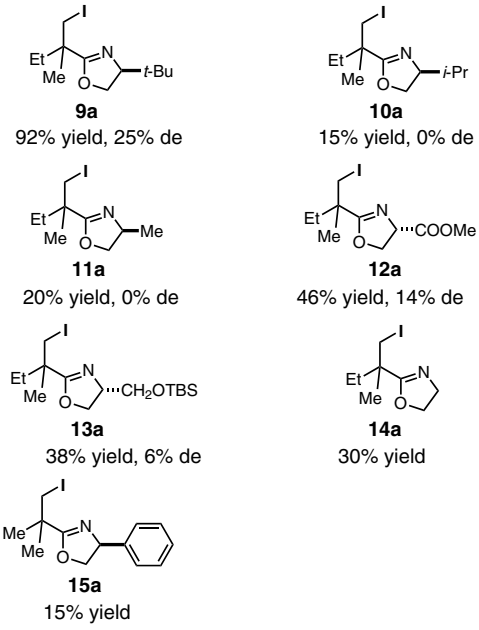
Table 1. Diastereoselective iodination[a]

Entry	Substrate	Product	Yield (%)	de (%)
1	 **16**	 **16a**	60[b]	35
2	 **17**	 **17a**	41[c]	55
3	 **18**	 **18a**	45[d]	55
4	 **19**	 **19a**	50[b]	25
5	 **20**	 **20a**	60[b]	10
6	 **21**	 **21a**	70[e]	0
7	 **22**	 **22a**	83[f]	82
8	 **23**	 **23a**	62[g]	87
9	 **24**	 **24a**	65[h]	99

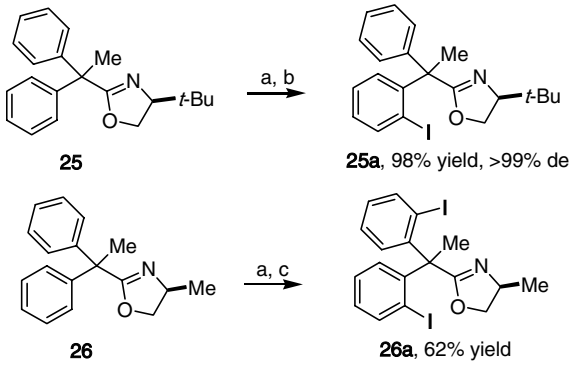
[a] Oxa = (*S*)-4-*tert*-Butyloxazoline-2-. Reaction conditions: $Pd(OAc)_2$ (10 mol %) I_2 (1 equiv), $PhI(OAc)_2$ (1 equiv), CH_2Cl_2.
[b] 65 °C, $PhI(OAc)_2$ (1 equiv) was added after 12 h, and stirring continued for another 24 h.
[c] 50 °C, 41 h.
[d] 24 °C, 42 h.
[e] 24 °C, 24 h.
[f] 24 °C, 30 h.
[g] 50 °C, 48 h.
[h] 24 °C, 96 h.

decrease in steric bulkiness of the 4-substituent in substrate **26** resulted in a complete loss of selectivity.

We observed that the iodination reaction can be influenced by the structures of oxazolines (Schemes 5 and 6). It is especially intriguing that oxazoline **10** exhibits poor reactivity in comparison with **9**.[17] To seek an explanation for this experimental observation, we decided to investigate how the methine C–H bond in **10** interacts with the Pd center. Since we were unable to obtain crystal structures in the form of $Pd(Oxa)_2(OAc)_2$ using substrates listed in the table, $Pd(Oxa)_2TFA_2$ **27a** was prepared by stirring oxazoline **27** with $Pd(TFA)_2$ in CH_2Cl_2 at room temperature. The crystal



Scheme 5. Ligand effect in iodination. Reagents and conditions: $Pd(OAc)_2$ (10 mol %), I_2 (1 equiv), $PhI(OAc)_2$ (1 equiv), CH_2Cl_2, 24 °C, 64 h (**9a**–**11a**, **14a** and **15a**); 50 °C, 48 h (**12a**–**13a**).



Scheme 6. Diastereoselective iodination of aryl C–H bonds. Reagents and conditions: (a) $Pd(OAc)_2$ (10 mol %), I_2 (1 equiv), $PhI(OAc)_2$ (1 equiv), CH_2Cl_2, 24 °C; (b) 13 h; (c) 48 h.

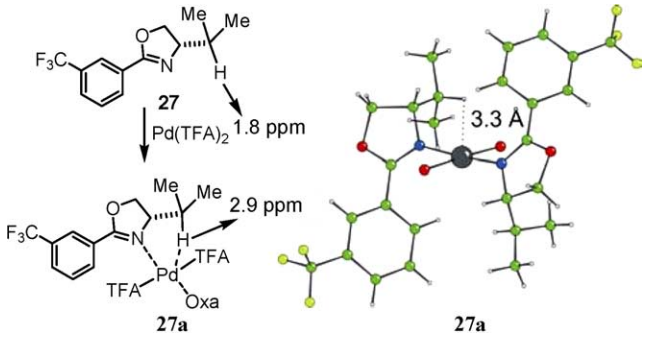


Figure 1.

structure showed that the methine C–H bond in the isopropyl group is pointing toward the Pd center (Fig. 1). A downfield shift of the methine proton from 1.8 to

2.9 ppm was also observed in the ^{1}H NMR. The downfield shift in ^{1}H NMR and the distance (H atoms were placed at idealized geometric positions) between the methine C–H bond and the Pd center in the crystal structure (**27a**)[18] rules out the possibility of agostic interactions.[19] However, a weaker interaction between Pt^{II} and C–H bonds reported by Pregosin was shown to result in a downfield shift.[20] At this stage, it is unclear to us as to how this interaction may interfere the C–H cleavage process. However, this preliminary study, in combination with the experimental results obtained using substrates **9**–**15** suggested that the C–H bonds in the vicinity of the σ-chelating group need to be appropriately positioned or avoided.

We are currently in the process of obtaining crystal structures of the Pd-alkyl intermediates using a wide range of prochiral oxazoline substrates. Further optimization of the oxazoline structures using the structural information will be carried out in our laboratory in order to improve the diastereoselectivity with a broad substrate scope.

Acknowledgments

We thank Brandeis University for financial support and the Camille and Henry Dreyfus Foundation for a New Faculty Award.

References

1. (a) Groves, J. T.; Viski, P. *J. Am. Chem. Soc.* **1989**, *111*, 8537–8538; (b) Punniyamurthy, T.; Katsuki, T. *Tetrahedron* **1999**, *55*, 9439–9454; (c) Zhou, X. G.; Yu, X. Q.; Huang, J. S.; Che, C. M. *Chem. Commun.* **1999**, 2377–2378; (d) Jang, D. O.; Kim, D. D.; Pyun, D. K.; Beak, P. *Org. Lett.* **2003**, *5*, 4155–4157; (e) Kennedy, M.; Mckervey, M. A.; Maguire, A. R.; Roos, G. H. P. *J. Chem. Soc., Chem. Commun.* **1990**, 361–362; (f) Doyle, M. P.; Protopopova, M. N.; Poulter, C. D.; Rogers, D. H. *J. Am. Chem. Soc.* **1995**, *117*, 7281–7282; (g) Espino, C. G.; When, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935–6936; (h) Davies, H. M. L.; Beckwith, R. E. *J. Chem. Rev.* **2003**, *103*, 2861–2903; (i) Muller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905–2919.
2. (a) Johnson, J. A.; Li, N.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 6900–6903; (b) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510–11511.
3. (a) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1699–1712; (b) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1999**, *121*, 6616–6623; (c) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826–834; (d) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077–1101.
4. (a) Bennett, M. A.; Milner, D. L. *J. Am. Chem. Soc.* **1969**, *91*, 6983–6994; (b) Ibers, J. A.; Dicosimo, R.; Whitesides, G. M. *Organometallics* **1982**, *1*, 13–20.
5. Ryabov, A. D. *Synthesis* **1985**, 233–252.
6. For various examples of stoichiometric cyclopalladation reactions, see: (a) Canty, A. J. In *Comprehensive Organometallic Chemistry II: A Review of the Literature 1982–1994*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon, 1995; pp 225–255; (b) Balavoine, G.; Clinet, J. C. *J. Organomet. Chem.* **1990**, *390*, C84–C88.
7. (a) Constable, A. G.; McDonald, W. G.; Sawjins, L. C.; Shaw, B. L. *J. Chem. Soc., Chem. Commun.* **1978**, 1061–1062; (b) Carr, K.; Sutherland, J. K. *J. Chem. Soc., Chem. Commun.* **1984**, 1227–1228; (c) Baldwin, J. E.; Jones, R. H.; Najera, C.; Yus, M. *Tetrahedron* **1985**, *41*, 699–711; (d) Bore, L.; Honda, T.; Gribble, G. W. *J. Org. Chem.* **2000**, *65*, 6278–6282.
8. (a) Gomez, M.; Granell, J.; Martinez, M. *Eur. J. Chem.* **2000**, 217–224; (b) Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527–2572.
9. (a) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542–9543; (b) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300–2301.
10. (a) Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *J. Am. Chem. Soc.* **1996**, *118*, 5961–5976; (b) Fekl, U.; Goldberg, K. I. *J. Am. Chem. Soc.* **2002**, *124*, 6804–6805.
11. (a) Canty, A. J.; Denney, M.; Koten, G.; Skelton, B. W.; White, A. H. *Organometallics* **2004**, *23*, 5432–5439; (b) Amijs, C. H. M.; Kleij, A. W.; van Klink, G. P. M.; Spek, A. L.; van Koten, G. *Organometallics* **2005**, *24*, 2773–2779.
12. Giri, R.; Chen, X.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112–2115.
13. For various protocols for the preparation of monodentate oxazolines see: Gomes, M.; Muller, G.; Rocamora, M. *Coord. Chem. Rev.* **1999**, *193–195*, 769–835.
14. For the early use of $PhI(OAc)_2$ as an oxidant for the acetoxylation of benzene, see: Yoneyama, T.; Crabtree, R. H. *J. Mol. Catal. A-Chem.* **1996**, *108*, 35.
15. Typical procedure: Oxazoline (1 mmol) was placed in a 20 mL scintillation vial and dissolved in CH_2Cl_2 (5 mL). Palladium acetate (22.4 mg, 0.1 mmol), iodobenzene diacetate (322 mg, 1 mmol) and iodine (253.8 mg, 1 mmol) were added to the solution. The vial was tightly sealed with a polypropylene lined cap and the resulting violet solution was either stirred at room temperature or heated at 50–65 °C until black palladium iodide precipitated out. The solvent was removed in a rotary evaporator. The product was purified by silica gel column chromatography eluting first with hexane to remove iodine and iodobenzene, and then with ethylacetate/hexane 1:20.
16. Eaton, P. E.; Daniels, R. G.; Casucci, D.; Cunkle, G. T. *J. Org. Chem.* **1987**, *52*, 2100–2102.
17. Murai has previously tested oxazolines as directing groups to activate ortho-aryl C–H bonds using a Ru(II) catalyst. It was concluded that a chiral oxazoline bearing a hydrogen α to the nitrogen is not suitable for C–H activation, due to the preferential oxidation of this hydrogen. For details see: Kakiuchi, F.; Sato, T.; Yamauchi, M.; Chatani, N.; Murai, S. *Chem. Lett.* **1999**, 19–20.
18. CCDC number 287801.
19. Crabtree, R. H.; Holt, E. M.; Lavin, M.; Morehouse, S. M. *Inorg. Chem.* **1985**, *24*, 1986–1992.
20. Pregosin, P. S.; Wombacher, F. *Magn. Reson. Chem.* **1991**, *29*, S106–S117.