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Enantioselective Conjugate Addition Employing 2-Heteroaryl Titanates and Zinc Reagents

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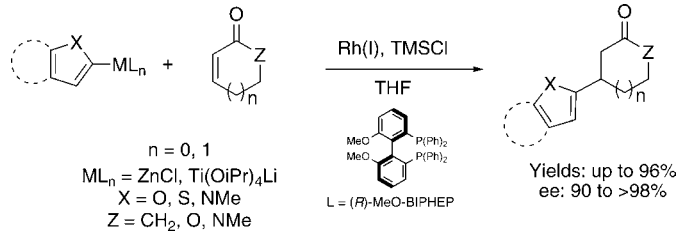
ABSTRACT



A general strategy for the conjugate addition of 2-heteroaryl nucleophiles to cyclic enones, unsaturated lactones, and unsaturated lactams in high enantioselectivities and yields is reported. The use of 2-heteroaryl titanates and zinc reagents offers a practical alternative to 2-heteroarylboronic acids, which are prone to undergo protodeboronation.

The development of methods to induce the catalytic enantioselective conjugate addition of aryl nucleophiles to Michael acceptors is an important objective in contemporary organic synthesis.[1] It is thus not surprising that extensive efforts over the past decade have led to the discovery of a number of useful techniques for inducing such constructions to form β-aryl carbonyl compounds in high yields and enantioselectivities. Indeed, electron-poor and electron-rich aryl groups may be transferred to α,β-unsaturated compounds in the presence of chiral Rh,[2] Pd,[3] and to a lesser extent, Cu[4] catalysts. Sources of aryl nucleophiles have included aryl boronic acids,[5] aryl titanates,[6] aryl trifluoroborates,[7] arylzinc chlorides,[2a,8] and aryl silicon[9] reagents. Of these, aryl boronic acids have been employed most frequently, likely in part due to their commercial availability.

In the context of an ongoing synthetic project in our group, we were interested in the enantioselective transfer of a furan-2-yl nucleophile to cyclopentenone. Although there are several reports of conjugate additions of furan nucleophiles to enones,[10] none of these are enantioselective. Indeed, at the time we initiated this research program, there were no examples of enantioselective conjugate additions involving 2-heteroaryl nucleophiles. The closest precedent was an example reported by Hayashi of the Rh-catalyzed enantioselective 1,4-addition of 3-thiopheneboronic acid to enones and enoates,[11] but these reactions suffer the disadvantage of requiring the use of a glovebox during setup. During the last

(1) (a) Tomioka, K.; Nagoaka, Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: New York, 1999; Vol. 3, Chapter 31. (b) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, UK, 1992. (c) Schmalz, H.-G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 4, Chapter 1.5.

(2) Selected examples include: (a) Hayashi, T.; Yamamoto, S.; Tokunaga, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 4224. (b) Yamamoto, Y.; Nishikata, T.; Miyaura, N. *J. Synth. Org. Chem., Jpn.* **2006**, *64*, 1112. (c) Kina, A.; Ueyama, K.; Hayashi, T. *Org. Lett.* **2005**, *7*, 5889. (d) Shintani, R.; Tokunaga, N.; Doi, H.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 6240. (e) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (f) Mariz, R.; Luan, X.; Gatti, M.; Linden, A.; Dorta, R. *J. Am. Chem. Soc.* **2008**, *130*, 2172.

(3) Selected examples include: (a) Gini, F.; Hessen, G.; Minnaard, A. J. *Org. Lett.* **2005**, *7*, 5309. (b) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Organometallics* **2004**, *23*, 4317. (c) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Chem. Commun.* **2004**, 1822. (d) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Chem. Lett.* **2005**, *34*, 720.

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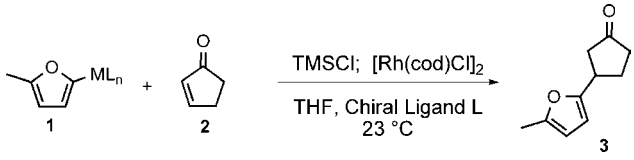
year, however, and concurrent with our own investigations, there have been two reports describing the enantioselective conjugate additions of 2-heteroaryl nucleophiles. Ishihara and co-workers described one example of a Rh-catalyzed enantioselective addition of 2-thiopheneboronic acid to a Michael acceptor.[12] Frost and co-workers employed thiophene-2-yl- and thiophene-3-ylzinc chloride as nucleophiles in Rh-catalyzed enantioselective conjugate additions to cyclic enones and 5,6-dihydro-2*H*-pyran-2-one.[13] Although this group also reported the addition of furan-2-ylzinc bromide to cyclohexenone and 5,6-dihydro-2*H*-pyran-2-one, these reactions proceeded in only 70 and 86% ee, respectively.

The early obstacle to using 2-heteroaryl nucleophiles in enantioselective conjugate additions likely arose because of the instability of 2-heteroarylboronic acids, which are known to undergo facile protodeboronation in transition-metal-catalyzed processes that employ water or alcohol as a cosolvent.[14] This problem has been very recently addressed by the development of air-stable 2-heterocyclic MIDA boronates by Burke and co-workers.[15] Although these boronates might be used in enantioselective Rh-catalyzed conjugate additions, facile preparation of these boronates is somewhat problematic.

Owing to the known difficulties associated with using 2-heteroarylboronic acids at the time we initiated this work, we screened the additions of readily available furan-2-yl organometallic reagents to 2-cyclopenten-1-one (**2**) in the presence of chiral transition metal catalysts. Some of these results using 5-methylfuran-2-ylzinc and titanate reagents **1** are summarized in Table 1. When 5-methylfuran-2-ylzinc chloride was used as the nucleophilic component, very good yields of the adduct **3** were obtained using $[Rh(cod)Cl]_2$ as the catalyst in the presence of a variety of chiral ligands; however, the enantioselectivity in all of these reactions was poor (Table 1, entries 1−6). On the other hand, we found that the corresponding furan-2-yl titanate reagent furnished the adduct **3** in both very good yield and enantioselectivity when BINAP-derived ligands were used (Table 1, entries 7 and 8); much lower yields of product were obtained using other chiral ligands (entries 9−11). The absolute stereochemistry of **3** was not determined.

We were somewhat surprised that the addition of 5-methylfuran-2-ylzinc chloride to **3** proceeded with such low enantioselectivity and wondered whether a background reaction was a contributing factor to the low ee observed in entries 1−6 (Table 1). Accordingly, several control experiments were performed. In the first of these, we discovered that the reaction of 5-methylfuran-2-ylzinc chloride with 2-cyclopenten-1-one occurred rapidly in the absence of the Rh(I) catalyst to provide **3** in 81% yield (Scheme 1). On the other hand, in a second control experiment using a 5-methylfuran-2-yl titanate, the yield of adduct was only 10% in the absence of the Rh(I) catalyst. Hence, the observed difference in ee for the Rh(I)-catalyzed additions of furylzinc and titanates in Table 1 is consistent with a significant background reaction for the former reagent.

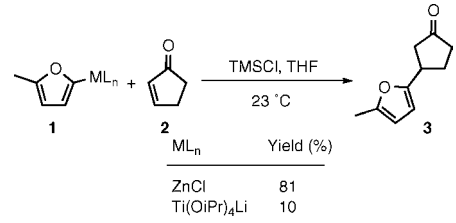
Table 1. Rh-Catalyzed Conjugate Addition of Furan-2-yl Titanate and Furan-2-ylzinc Chloride to 2-Cyclopenten-1-one[a]



entry	ML$_n$	ligand	yield (%)[b]	ee (%)[c,d]
1	ZnCl	(*S*)-BINAP	80	0
2	ZnCl	(*S*)-DIOP	83	0
3	ZnCl	(*S*,*S*)-DIPAMP	87	0
4	ZnCl	(*R*,*R*)-Jacobsen Ligand	75	0
5	ZnCl	(*R*)-Tol-BINAP	88	0
6[e]	ZnCl	(*S*)-BINAP	83	18
7	Ti(OiPr)$_4$Li	(*R*)-Tol-BINAP	84	90
8	Ti(OiPr)$_4$Li	(*S*)-BINAP	85	84
9	Ti(OiPr)$_4$Li	(*S*,*S*)-DIOP	5	*f*
10	Ti(OiPr)$_4$Li	(*S*,*S*)-DIPAMP	10	*f*
11	Ti(OiPr)$_4$Li	(*R*,*R*)-Jacobsen Ligand	5	*f*

[a] Reaction conditions: 10 mol % of $[Rh(cod)Cl]_2$, 0.75 mmol of TMSCl, ligand/Rh (1.1:1), 1.0 mmol of furan-2-ylzinc chloride or furan-2-yl titanate, 0.5 mmol of 2-cyclopenten-1-one. [b] Isolated yield of **3** after flash chromatography. [c] Determined by HPLC analysis (OD-H chiral column, 98:2 hexanes/2-propanol, 0.5 mL/min). [d] HPLC analysis was performed on the four diastereomeric alcohol derivatives of the product, formed by $NaBH_4$ reduction of **3**. [e] Slow addition of the nucleophile (2 mmol/h). [f] Not evaluated due to unsatisfactory chemical yield.

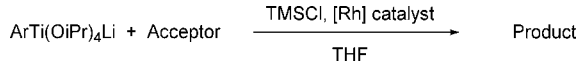
Scheme 1. Background Reaction

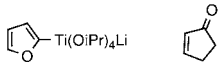
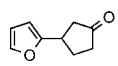
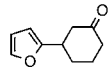
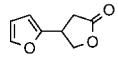
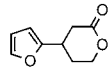
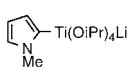
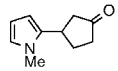
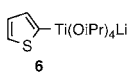
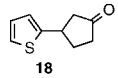
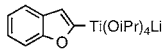
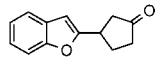
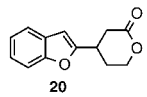
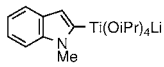
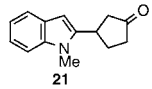
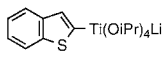
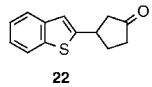


The series of experiments summarized in Table 1 established the viability of furan-2-yl titanates as nucleophiles in enantioselective 1,4-additions, but the catalyst loadings were rather high. We then discovered that using $[Rh(C_2H_4)_2Cl]_2$ (Table 2, entry 1) as the precatalyst with (*R*)-Tol-BINAP enabled us to reduce the loading without compromising the yield or enantioselectivity. We then began to probe the scope of this method by examining the reactions of other heteroaryl titanates and Michael acceptors. We quickly discovered that the conditions that we had developed for the additions of furan-2-yl titanates to cyclopentenone required some adjustments when other heteroaryl titanates were employed. For example, when benzofuran-2-yl titanate was added to 2-cyclopenten-1-one (**2**) under conditions that had been optimized for the addition of **4** to **2**, the adduct **19** was formed in high ee but low yield (Table 2, entry 8). Subsequent screening of rhodium precatalysts and ligands led to the finding that the catalyst system derived from [Rh(cod)acac] and (*R*)-MeO-BIPHEP was superior (Table 2, entries 8 and 9).

With the newly optimized conditions thus established, we explored the reactions of a number of heteroaryl titanates

Table 2. Enantioselective Conjugate Additions of 2-Heteroaryl Titanates to Michael Acceptors[a]



entry	ArTi(OiPr)$_4$Li	acceptor	product	yield (%)[b]	ee (%)[c]
1[d]	 **4**	**2**	 **13**	90	90[e]
2	**4**	**2**	**13**	90	98[e]
3	**4**	 **10**	 **14**	60	94[e]
4	**4**	 **11**	 **15**	60	>98
5	**4**	 **12**	 **16**	42	97
6[f]	 **5**	**2**	 **17**	43	93
7	 **6**	**2**	 **18**	60	95[e]
8[d]	 **7**	**2**	 **19**	37	90
9	**7**	**2**	**19**	96	>98
10	**7**	**12**	 **20**	70	>98
11	 **8**	**2**	 **21**	47	90
12	 **9**	**2**	 **22**	69	95

[a] Reaction conditions: 10 mol % of [Rh], Rh/L (1:1.1), [Rh] = [Rh(cod)acac]; L = (*R*)-MeO-BIPHEP, 0.45 mmol of TMSCl, 0.30 mmol of Michael acceptor, 0.6 mmol of 2-heteroaryl titanate, THF (−78 °C → rt). [b] Isolated yield after flash chromatography. [c] Determined by HPLC analysis (OD-H or AD chiral column). [d] [Rh] = 5 mol % of $[Rh(C_2H_4)_2Cl]_2$, L = (*R*)-Tol-BINAP. [e] HPLC analysis was performed on the four diastereomeric alcohol derivatives of the product, formed by $NaBH_4$ reduction of the product. [f] TESCl was employed as the Lewis acid.

and acceptors (Table 2). In the event, we found that pyrrol-2-yl, benzofuran-2-yl, benzothiophene-2-yl, furan-2-yl, thiophene-2-yl, and indol-2-yl titanates added to a variety of Michael acceptors in moderate to excellent yield and high ee (Table 2). In view of the modest enantioselectivity reported by Frost for the addition of thiophene-2-ylzinc reagents to 2-cyclopenten-1-one (**2**),[13] it is noteworthy that the corresponding titanate added to **2** in excellent ee (Table 2, entry 7). Although the additions to both cyclic enones and unsaturated lactones proceeded efficiently, the reactions of enones typically furnished higher yields of adducts than enoates.

In an attempt to extend the substrate scope to α-substituted enones, we examined the use of 2-methyl-2-cyclopenten-1-one as a substrate, although there are few examples of such acceptors in transition-metal-catalyzed 1,4-additions.[1−9] Hence, perhaps not surprisingly, we found in a preliminary experiment that furan-2-yl titanate did not add to 2-methyl-2-cyclopenten-1-one under our standard conditions. We did, however, develop an expedient solution to this problem. Namely, when TESCl was employed as the Lewis acid instead of TMSCl, it was possible to isolate the silyl enol ether of the conjugate addition product. The enolate generated in situ from this intermediate could then be trapped with MeI to give 3-(furan-2-yl)-2-methylcyclopentanone as a single diastereomer, the relative stereochemistry of which was not unequivocally determined.

During the course of these studies, we observed that the yields of the additions of heteroaryl titanates to α,β-unsaturated carbonyl compounds were sometimes lower than desired, even though the enantioselectivities in these reactions were consistently high. We had discovered that furan-2-ylzinc chloride added readily to 2-cyclopenten-1-one in the absence of a chiral catalyst, but we did not know whether such background reactions would undermine the additions of other heteroarylzinc reagents to Michael acceptors. Accordingly, in those cases where the conjugate additions of titanates to unsaturated carbonyl compounds were low yielding, the reaction of the corresponding heteroarylzinc reagent was examined. We screened several rhodium precatalysts and

(4) (a) Lee, K.-S.; Brown, M. K.; Hird, A. W.; Hoveyda, A. *J. Am. Chem. Soc.* **2006**, *128*, 7182. (b) May, T. L.; Brown, M. K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7358. (c) Robert, T.; Velder, J.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2008**, *47*, 7718. (d) Hawner, C.; Li, K.; Cirriez, V.; Alexakis, A. *Angew. Chem.* **2008**, *47*, 8211.

(5) Selected examples include: (a) Kurihara, K.; Sugishita, N.; Oshita, K.; Piao, D.; Yamamoto, Y.; Miyaura, N. *J. Organomet. Chem.* **2007**, *692*, 428. (b) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *Org. Synth.* **2002**, *79*, 84. (c) Takaya, Y.; Ogasawara, M.; Hayashi, T. *Chirality* **2000**, *12*, 469. (d) Kuriyama, M.; Tomioka, K. *Tetrahedron Lett.* **2001**, *42*, 921. (e) Kuriyama, M.; Nagai, K.; Yamada, K.-I.; Miwa, Y.; Taga, T.; Tomioka, K. *J. Am. Chem. Soc.* **2002**, *124*, 8932.

(6) (a) Tokunaga, N.; Yoshida, K.; Hayashi, T. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5445. (b) Hayashi, T.; Tokunaga, N.; Yoshida, K.; Han, J. W. *J. Am. Chem. Soc.* **2002**, *124*, 12102. (c) Yoshida, K.; Hayashi, T. *J. Am. Chem. Soc.* **2003**, *125*, 2872.

(7) (a) Darses, S.; Genet, J.-P. *Eur. J. Org. Chem.* **2003**, 4313. (b) Pucheault, M.; Darses, S.; Genet, J.-P. *Eur. J. Org. Chem.* **2002**, 3552. (c) Pucheault, M.; Darses, S.; Genet, J.-P. *Tetrahedron Lett.* **2002**, *43*, 6155.

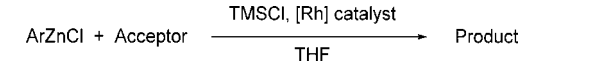
(8) Shintani, R.; Tokunaga, N.; Doi, H.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 6240.

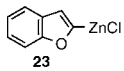
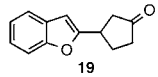
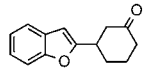
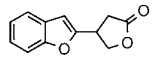
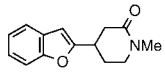
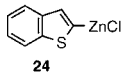
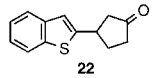
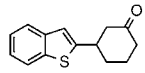
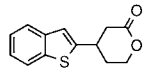
(9) Oi, S.; Taira, A.; Honma, Y.; Inoue, Y. *Org. Lett.* **2003**, *5*, 97.

(10) (a) Ng, J. S.; Behling, J. R.; Campbell, A. L.; Nguyen, D.; Lipshutz, B. *Tetrahedron Lett.* **1988**, *29*, 3045. (b) Kraus, G. A.; Gottschalk, T. *Tetrahedron Lett.* **1983**, *29*, 2727. (c) Jones, P.; Reddy, C. K.; Knochel, P. *Tetrahedron* **1998**, *54*, 1471. (d) Lin, Y.-D.; Kao, J.-Q.; Chen, C.-T. *Org. Lett.* **2007**, *9*, 5195.

(11) Yoshida, K.; Hayashi, T. *Heterocycles* **2003**, *59*, 605.

Table 3. Enantioselective Conjugate Addition of 2-Heteroarylzinc Nucleophiles to Michael Acceptors[a]



entry	ArZnCl	acceptor	product	yield (%)[b]	ee (%)[c]
1	 **23**	 **2**	 **19**	91	91
2	**23**	 **10**	 **26**	93	90
3	**23**	 **11**	 **27**	64	98
4	**23**	 **25**	 **28**	62	91
5	 **24**	**2**	 **22**	75	98
6	**24**	**10**	 **29**	92	>98
7	**24**	 **12**	 **30**	47	>98

[a] Reaction conditions: 10 mol % of [Rh], Rh:L (1:1.1), [Rh] = [Rh(cod)acac]; L = (*R*)-MeO-BIPHEP, 0.45 mmol of TMSCl, 0.30 mmol of Michael acceptor, 0.6 mmol of 2-heteroarylzinc chloride in THF (−78 °C → rt). [b] Isolated yield after flash chromatography. [c] Determined by HPLC analysis (OD-H chiral column).

chiral ligands (e.g., (*R*)-Tol-BINAP, Josiphos, Walphos, and Carreira's diene) and again found that the catalyst system derived from [Rh(cod)acac] and (*R*)-MeO-BIPHEP was highly effective and promoted the enantioselective addition of benzofuran-2-ylzinc chloride (**23**) to 2-cyclopenten-1-one (**2**) in 91% yield and 91% ee (Table 3, entry 1).

Because this result was nearly as good as the reaction using benzofuran-2-yl titanate (cf. Table 2, entry 9), we extended this reaction of **23** to other cyclic enones and unsaturated lactones and lactams, and these conjugate additions typically also proceeded with excellent enantioselectivities (Table 3, entries 2−4). Similarly, benzothiophene-2-ylzinc chloride (**24**) added to several Michael acceptors in ≥98% ee (Table 3, entries 5−7).

In summary, a variety of 2-heteroaryl titanate and zinc reagents added to cyclic enones, unsaturated lactones, and lactams in moderate to excellent yields and high enantioselectivities. In some cases, the yields and enantioselectivities in the conjugate additions of heteroaryl titanate and zinc reagents were comparable (cf. Table 2, entries 9 and 12, and Table 3, entries 1 and 5). However, in most cases involving furan and in preliminary experiments using *N*-methylpyrrole and *N*-methylindole, higher enantioselectivities were obtained using the titanate reagents. The application of this new methodology to the synthesis of complex natural products is the subject of current investigations, the results of which will be reported in due course.

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Supporting Information Available: Experimental procedures, chromatographic data, and characterization and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Konno, T.; Tanaka, T.; Miyabe, T.; Morigaki, A.; Ishihara, T. *Tetrahedron Lett.* **2008**, *49*, 2106.
(13) Le Notre, J.; Allen, J. C.; Frost, C. G. *Chem. Commun.* **2008**, 3795.
(14) (a) Buchwald, S.; Billingsley, K. *J. Am. Chem. Soc.* **2007**, *129*, 3358. (b) Lautens, M.; Mancuso, J. *J. Org. Chem.* **2004**, *69*, 3478. (c) Chao, J.; Ling, Y.; Liu, X.; Luo, X.; Brodie, A. M. H. *Steroids* **2006**, *71*, 585.
(15) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961.