DOI: 10.1002/anie.200701201

Asymmetric Arylation

Highly Enantioselective Aryl Additions of [$AlAr_3$(thf)] to Ketones Catalyzed by a Titanium(IV) Catalyst of (*S*)-Binol[**]

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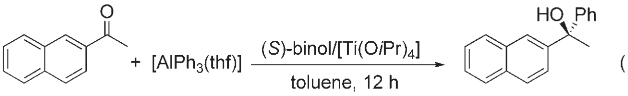
The asymmetric catalytic C–C bond formation by addition of an organozinc reagent to aldehydes for the synthesis of enantiomerically pure secondary alcohols as building blocks for bioactive compounds has been extensively studied, and numerous catalytic systems have been developed to yield excellent enantioselectivities.[1] Since tertiary alcohols appear in bioactive compounds,[2] the construction of chiral quaternary carbon centers is synthetically important owing to the inertness of ketones toward additions of carbon nucleophiles and less differentiation of the two groups attached to the carbonyl carbon atom. Despite efforts in recent years, only limited examples of catalytic asymmetric additions to ketones have been reported to give excellent stereoselectivities. Organozinc compounds have been used for asymmetric additions of alkyl compounds to ketones[3] or α-ketoesters[4] and for additions of vinyl,[5] alkynyl,[2c,6] or aryl compounds[7] to ketones. For allyl addition reactions, the considerably toxic allyl tin compounds have been the commonly used reagents,[8] and in fewer cases, allyl silicon[2e,9] or allyl boron compounds[10] have been used. In addition to these reagents, organoaluminum compounds are excellent nucleophiles for organic reactions[11] owing their high reactivities, a greater Lewis acidity of the aluminum center, and low toxicities. However, the use of organoaluminum compounds in asymmetric catalysis is rare. In the past few years, asymmetric catalytic alkylation,[12] allylation,[13] and alkynylation[14] reactions employing organoaluminum reagents have been established to achieve good to excellent enantioselectivities. Recently, we demonstrated that the novel [$AlAr_3$(thf)] reagents are powerful aryl nucleophiles for additions to aldehydes catalyzed by the titanium catalyst of (*R*)-H_8-binol (binol = 2,2′-dihydroxy-1,1′-binaphthyl) with the reactions complete in only 10 min.[15]

In studies of asymmetric aryl additions to ketones,[7] only a few papers have been reported in just two catalytic systems. The first system is a zinc catalyst of (+)-daib (3-*exo*-(dimethylamino)isoborneol) with which direct additions of the $ZnPh_2$ reagent afford phenylation products.[7a] The second system is a series of titanium catalysts of disulfonamides[16] with which additions of $ZnPh_2$ or aryl zinc reagents furnish phenylation or arylation products.[7b–f] However, generation of aryl zinc reagents from excess $ZnEt_2$ and aryl boron compounds requires reaction conditions at elevated temperatures for 12–16 h. Furthermore, the arylation reactions have not reached a satisfactory level in yields and stereoselectivities.[7f] To extend applications of [$AlAr_3$(thf)] reagents in catalysis, we report herein the first example of asymmetric aryl additions of organoaluminum reagents to ketones. The (*S*)-binol molecule was selected as the ligand since binol is a remarkable ligand applied to many varieties of asymmetric reactions[17] and since dititanium complexes of binol ligands with known structures[18] catalyze dialkyl zinc additions to aldehydes via an alkyl titanium species.[18a] Furthermore, both (*R*)- and (*S*)-binol ligands are commercially available and are currently considerably inexpensive. Optimizations of reaction conditions were conducted on 2′-acetonaphthone with catalytic systems generated from mixing (*S*)-binol and [Ti(O*i*Pr)$_4$] [Eq. (1)], with the results summarized in Table 1. In the presence of 10 mol% (*S*)-binol and one equivalent of both [Ti(O*i*Pr)$_4$] and [$AlPh_3$(thf)] at 0 °C, the reaction afforded the tertiary alcohol in 12 h in only 29% yield with an enantioselectivity of 77% *ee* (Table 1, entry 1). Increasing the



(1)

Table 1: Optimization of [$AlPh_3$(thf)] additions to 2′-acetonaphthone catalyzed by in situ formed (*S*)-binol/[Ti(O*i*Pr)$_4$] systems.[a,b]

Entry	Equiv [$AlPh_3$(thf)]	Equiv [Ti(O*i*Pr)$_4$]	Yield [%][c]	*ee* [%][d]
1	1.0	1.0	29	77
2	1.5	1.0	20	38
3	2.5	1.0	21	24
4	2.5	1.8	29	53
5	2.5	3.4	90	83
6	2.5	5.0	87	93
7	2.5	6.0	77	87
8	1.5	5.0	66	84
9	3.0	5.0	94	89
10[e]	2.5	5.0	98	78
11[f]	2.5	5.0	66	91
12[g]	2.5	5.0	31	79
13[h]	2.5	5.0	36	82

[a] 0.50 mmol 2′-acetonaphthone, 0.050 mmol (*S*)-binol; toluene (6 mL), 0 °C. [b] Equivalents of [$AlPh_3$(thf)] and [Ti(O*i*Pr)$_4$] relative to 2′-acetonaphthone. [c] Yields are based on ^{1}H NMR spectra. [d] The *ee* values were determined by HPLC using a chiral OJ column from Daicel. [e] 25 °C. [f] 5 mol% (*S*)-binol. [g] In CH_2Cl_2. [h] In THF.

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[**] Financial support from the National Science Council of Taiwan, ROC, under the grant number NSC 95-2113-M-005-011, is appreciated.

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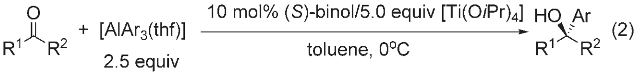
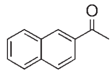
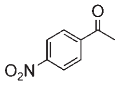
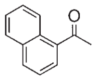
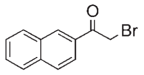
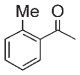
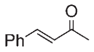
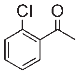
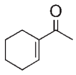
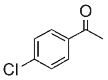
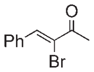
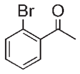
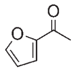
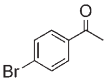
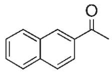
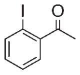
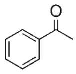
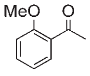
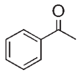
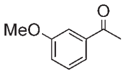
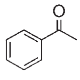
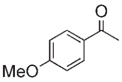
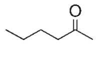
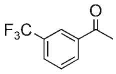
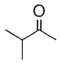
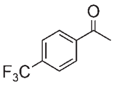
amount of [AlPh$_3$(thf)] to 1.5 and 2.5 equiv afforded the product in low yields and low enantioselectivities (Table 1, entries 2 and 3). While keeping [AlPh$_3$(thf)] at 2.5 equiv and tuning the amount of [Ti(O*i*Pr)$_4$] to 1.8, 3.4, and 5.0 equiv, enantioselectivities increase from 24 % *ee* to 53 %, 83 %, and 93 % *ee*, respectively (Table 1, entries 4–6).[19] Increasing the amount of [Ti(O*i*Pr)$_4$] further to 6.0 equiv gave the product in 77 % yield and 87 % *ee* (Table 1, entry 7). Keeping the amount of [Ti(O*i*Pr)$_4$] at 5.0 equiv but tuning the amount of [AlPh$_3$(thf)] to 1.5 and 3.0 equiv afforded the product in yields of 66 % and 94 % and enantioselectivities of 84 % and 89 % *ee* (Table 1, entries 8 and 9). When the reaction was conducted at 25 °C, the product was obtained in the highest yield (98 %) but in a lower enantioselectivity of 78 % *ee* (Table 1, entry 10). Reducing the amount of (*S*)-binol to 5 mol % furnished the product in a moderate yield of 66 % with 91 % *ee* (Table 1, entry 11). When the reaction was carried out in CH$_2$Cl$_2$ (Table 1, entry 12) or in THF (entry 13), the product was obtained in low yields of 31 % and 36 %.

To demonstrate generalities of the best catalytic system, aryl additions to aromatic, α,β-unsaturated, and aliphatic ketones [Eq. (2)] were conducted, and the results are listed in Table 2. For aromatic ketones (Table 2, entries 1–15), [AlPh$_3$(thf)] additions afforded tertiary alcohols in excellent enantioselectivities of 90 % *ee* or greater, except for substrates of 2′-methoxyacetophenone (30 % ee, entry 9), 3′-methoxyacetophenone (77 % *ee*, entry 10), 3′-(trifluoromethyl)acetophenone (85 % *ee*, entry 12), and α-bromo-2′-acetonaphthone (82 % *ee*, entry 15). It was found that additions to the more hindered ketones proceed sluggishly and require longer reaction times to furnish products in satisfactory yields. For example, the phenyl addition to 1′-acetonaphthone in 36 h afforded the product in only 38 % yield (Table 2, entry 2), and the addition to 2′-bromoacetophenone gave the product in



(2)

Table 2: Asymmetric [AlAr$_3$(thf)] addition to ketones catalyzed by 5.0 equiv [Ti(O*i*Pr)$_4$] with 10 mol % (*S*)-binol.[a]

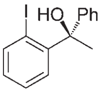
Entry	Substrate	Ar	*t* [h]	Yield [%][b]	*ee* [%][c]	Entry	Substrate	Ar	*t* [h]	Yield [%][b]	*ee* [%][c]
1		Ph	12	85	93	14		Ph	12	97	93
2		Ph	36	38	90	15		Ph	12	90	82[d]
3		Ph	12	35	90	16		Ph	12	96	87
4		Ph	12	73	97	17		Ph	12	93	91[d]
5		Ph	12	92	93	18		Ph	24	91	87[d]
6		Ph	36	50	97	19		Ph	16	95	84[d]
7		Ph	12	90	93	20		4-MeC$_6$H$_4$	12	94	91
8		Ph	168	50	96 (*R*)	21		2-naphthyl	12	81	90
9		Ph	12	98	30	22		4-TMSC$_6$H$_4$	12	91	93
10		Ph	36	74	77	23		4-MeOC$_6$H$_4$	12	87	78
11		Ph	36	97	93	24		Ph	12	67	19
12		Ph	12	91	85	25		Ph	36	37	33
13		Ph	12	98	92						

[a] 0.50 mmol ketone, 0.050 mmol (*S*)-binol, 1.25 mmol [AlAr$_3$(thf)], 2.5 mmol [Ti(O*i*Pr)$_4$], toluene, 0 °C. [b] Yields of isolated product. [c] The *ee* values were determined by HPLC using chiral columns from Daicel. [d] 20 mol % (*S*)-binol. TMS = trimethylsilyl.

50% yield (Table 2, entry 6). The above results reveal minimal effects of substituents and substituted positions on the aromatic group in terms of stereoselectivities. However, the reactivity is rather sensitive to steric hindrance of the substrates.

Notably, the addition to 2′-methoxyacetophenone afforded the product in an excellent yield of 98%, but with a low enantioselectivity of 30% *ee* (Table 2, entry 9). The high yield is attributed to the chelate effect of the substrate, which facilitates the coordination of 2′-methoxyacetophenone to the active metal center. However, the chelation lowers the enantioselectivity. For 3′- and 4′-methoxyacetophenones with the methoxy substituent oriented away from the carbonyl group, enantioselectivities improve to 77 and 93% *ee* (Table 2, entries 10 and 11). For these two substrates, longer reaction times of 36 h are required to afford products in moderate to excellent yields of 74% and 97%.

To determine the absolute configurations of the phenylation products, the addition of the phenyl group to 2′-iodoacetophenone was carried out, furnishing 1-phenyl-1-(2-iodophenyl)ethanol ((*R*)-**1**) after seven days in 50% yield with a superb enantioselectivity of 96% *ee* (Table 2, entry 8). The absolute configuration of (*R*)-**1** was determined by comparing the optical rotation with the resolved compound.[20] It is assumed that aromatic ketones coordinate to the active metal center in the same orientation.



(*R*)-**1**

For α,β-unsaturated ketones and 2-acetylfuran, good to excellent enantioselectivities of 84 to 91% *ee* (Table 2, entries 16–19) were obtained. Notably, the tertiary alcohol obtained from the phenyl addition to 2-acetylfuran (Table 2, entry 19) is an important intermediate leading to a wide variety of bioactive compounds.[21] Additions of different aryl compounds, such as 2-naphthyl, 4-tolyl, or 4-(trimethylsilyl)-phenyl, to aromatic ketones were carried out and gave the desired products in high yields with excellent enantioselectivities of 90 to 93% *ee* (Table 2, entries 20–22). In contrast, the 4-methoxyphenyl addition to acetophenone afforded the product in a good yield of 87% but with a moderate enantioselectivity of 78% *ee* (Table 2, entry 23). The aryl additions to acetophenone (Table 2, entries 21 and 23) afforded products in an opposite absolute configuration relative to products derived from the phenyl addition to aryl ketones. In this study, two examples of the phenyl addition to aliphatic ketones were examined. However, products were obtained in low yields and poor enantioselectivities (Table 2, entries 24 and 25).

In summary, novel asymmetric aryl additions of [$AlAr_3$(thf)] to ketones by catalysis with a titanium catalyst of (*S*)-binol are reported. A wide variety of ketones were examined to afford products, in general, in excellent enantioselectivities of 90% *ee* or greater for aromatic ketones bearing either an electron-donating or an electron-withdrawing substituent at the 2′-, 3′-, or 4′-position on the aromatic ring. Steric effects were observed for additions to *ortho*-substituted aromatic ketones in that longer reaction times were required to give products in higher yields. The catalytic system applies also to α,β-unsaturated ketones and 2-acetylfuran to give products in good to excellent enantioselectivities. More importantly, aluminum reagents with different aryl nucleophiles can be easily prepared for additions to aromatic ketones, furnishing tertiary diaryl alcohols in both absolute configurations. Further investigations of organoaluminum reagents in catalysis are currently underway.

Experimental Section

In a dry nitrogen atmosphere, (*S*)-binol (0.0143 g, 0.0500 mmol) and [Ti(O*i*Pr)$_4$] (0.75 mL, 2.5 mmol) were mixed in dry toluene (1 mL) at room temperature. After stirring the mixture for 1 h, a solution of [$AlAr_3$(thf)] (1.25 mmol) in toluene (5 mL) was added at 0°C. The mixture was stirred for another 30 min before addition of a ketone (0.50 mmol). The mixture was stirred at 0°C and quenched with 1 M aqueous HCl. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography to give the tertiary alcohol. Enantiomeric excess of the products was determined by HPLC using chiral columns from Daicel.

Received: March 19, 2007

Keywords: aluminum · asymmetric synthesis · homogeneous catalysis · ketones · titanium

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[1] a) L. Pu, H.-B. Yu, *Chem. Rev.* **2001**, *101*, 757; b) D. J. Ramón, M. Yus, *Chem. Rev.* **2006**, *106*, 2126.

[2] a) H. Lebel, E. N. Jacobsen, *J. Org. Chem.* **1998**, *63*, 9624; b) Y. Hayakawa, J. W. Kim, H. Adachi, K. Shin-ya, K.-i. Fujita, H. Seto, *J. Am. Chem. Soc.* **1998**, *120*, 3524; c) G. Lu, X. Li, X. Jia, W. L. Chan, A. S. C. Chan, *Angew. Chem.* **2003**, *115*, 5211; *Angew. Chem. Int. Ed.* **2003**, *42*, 5057; d) R. Shintani, M. Inoue, T. Hayashi, *Angew. Chem.* **2006**, *118*, 3431; *Angew. Chem. Int. Ed.* **2006**, *45*, 3353; e) N. Z. Burns, B. M. Hackman, P. Y. Ng, I. A. Powelson, J. L. Leighton, *Angew. Chem.* **2006**, *118*, 3895; *Angew. Chem. Int. Ed.* **2006**, *45*, 3811.

[3] a) D. J. Ramón, M. Yus, *Tetrahedron Lett.* **1998**, *39*, 1239; b) M. Yus, D. J. Ramón, O. Prieto, *Eur. J. Org. Chem.* **2003**, 2745; c) S.-J. Jeon, P. J. Walsh, *J. Am. Chem. Soc.* **2003**, *125*, 9544; d) S.-J. Jeon, H. Li, P. J. Walsh, *J. Am. Chem. Soc.* **2005**, *127*, 16416.

[4] a) E. F. DiMauro, M. C. Kozlowski, *J. Am. Chem. Soc.* **2002**, *124*, 12668; b) K. Funabashi, M. Jachmann, M. Kanai, M. Shibasaki, *Angew. Chem.* **2003**, *115*, 5647; *Angew. Chem. Int. Ed.* **2003**, *42*, 5489.

[5] a) H. Li, P. J. Walsh, *J. Am. Chem. Soc.* **2004**, *126*, 6538; b) H. Li, P. J. Walsh, *J. Am. Chem. Soc.* **2005**, *127*, 8355.

[6] a) L. Pu, *Tetrahedron* **2003**, *59*, 9873, and references therein; b) P. G. Cozzi, *Angew. Chem.* **2003**, *115*, 3001; *Angew. Chem. Int. Ed.* **2003**, *42*, 2895; c) P. G. Cozzi, S. Alesi, *Chem. Commun.* **2004**, 2448; d) C. Chen, L. Hong, Z.-Q. Xu, L. Liu, R. Wang, *Org. Lett.* **2006**, *8*, 2277.

[7] a) P. I. Dosa, G. C. Fu, *J. Am. Chem. Soc.* **1998**, *120*, 445; b) O. Prieto, D. J. Ramón, M. Yus, *Tetrahedron: Asymmetry* **2003**, *14*, 1955; c) C. García, P. J. Walsh, *Org. Lett.* **2003**, *5*, 3641; d) H. Li, C. García, P. J. Walsh, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5425; e) D. J. Ramón, M. Yus, *Angew. Chem.* **2004**, *116*, 286; *Angew. Chem. Int. Ed.* **2004**, *43*, 284; f) V. J. Forrat, O. Prieto, D. J. Ramón, M. Yus, *Chem. Eur. J.* **2006**, *12*, 4431; V. J. Forrat, O. Prieto, D. J. Ramón, M. Yus, *Chem. Eur. J.* **2006**, *12*, 6727.

[8] a) S. E. Denmark, J. Fu, *Chem. Rev.* **2003**, *103*, 2763, and references therein; b) J. G. Kim, K. M. Waltz, I. F. Garcia, D.

Kwiatkowski, P. J. Walsh, *J. Am. Chem. Soc.* **2004**, *126*, 12580; c) A. Cunningham. V. Mokal-Parekh, C. Wilson, S. Woodward, *Org. Biomol. Chem.* **2004**, *2*, 741; d) J. Lu, M.-L. Hong, S.-J. Ji, Y.-C. Teo, T.-P. Loh, *Chem. Commun.* **2005**, 4217.

[9] M. Wadamoto, H. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 14556.

[10] a) R. Wada, K. Oisaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 8910; b) E. Canales, K. G. Prasad, J. A. Soderquist, *J. Am. Chem. Soc.* **2005**, *127*, 11572.

[11] a) T. Ooi, M. Takahashi, K. Maruoka, *Angew. Chem.* **1998**, *110*, 875; *Angew. Chem. Int. Ed.* **1998**, *37*, 835; b) T. Ishikawa, A. Ogawa, T. Hirao, *J. Am. Chem. Soc.* **1998**, *120*, 5124; c) C. Spino, C. Beaulieu, *Angew. Chem.* **2000**, *112*, 2006; *Angew. Chem. Int. Ed.* **2000**, *39*, 1930; d) J. D. Rainier, J. M. Cox, *Org. Lett.* **2000**, *2*, 2707; e) K. Haraguchi, Y. Kubota, H. Tanaka, *J. Org. Chem.* **2004**, *69*, 1831; f) B. Wang, M. Bonin, L. Micouin, *Org. Lett.* **2004**, *6*, 3481; g) M. Uchiyama, H. Naka, Y. Matsumoto, T. Ohwada, *J. Am. Chem. Soc.* **2004**, *126*, 10526; h) K. Kojima, M. Kimura, Y. Tamaru, *Chem. Commun.* **2005**, 4717.

[12] a) A. S. C. Chan, F.-Y. Zhang, C.-W. Yip, *J. Am. Chem. Soc.* **1997**, *119*, 4080; b) B. L. Pagenkopf, E. M. Carreira, *Tetrahedron Lett.* **1998**, *39*, 9593; c) K. Biswas, O. Prieto, P. J. Goldsmith, S. Woodward, *Angew. Chem.* **2005**, *117*, 2272; *Angew. Chem. Int. Ed.* **2005**, *44*, 2232; d) M. d'Augustin, L. Palais, A. Alexakis, *Angew. Chem.* **2005**, *117*, 1400; *Angew. Chem. Int. Ed.* **2005**, *44*, 1376.

[13] J.-S. You, S.-H. Hsieh, H.-M. Gau, *Chem. Commun.* **2001**, 1546.

[14] Y.-S. Kwak, E. J. Corey, *Org. Lett.* **2004**, *6*, 3385.

[15] K.-H. Wu, H.-M. Gau, *J. Am. Chem. Soc.* **2006**, *128*, 14808.

[16] C. Garcia, L. K. LaRochelle, P. J. Walsh, *J. Am. Chem. Soc.* **2002**, *124*, 10970.

[17] J. M. Brunel, *Chem. Rev.* **2005**, *105*, 857.

[18] a) J. Balsells, T. J. Davies, P. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2002**, *124*, 10336; b) K. M. Waltz, P. J. Carroll, P. J. Walsh, *Organometallics* **2004**, *23*, 127.

[19] a) F.-Y. Zhang, C.-W. Yip, R. Cao, A. S. C. Chan, *Tetrahedron: Asymmetry* **1997**, *8*, 585; b) M. Mori, T. Nakai, *Tetrahedron Lett.* **1997**, *38*, 6233.

[20] G. A. Rabah, G. F. Koser, *Tetrahedron Lett.* **1996**, *37*, 6453.

[21] E. A. Couladouros, A. T. Strongilos, *Angew. Chem.* **2002**, *114*, 3829; *Angew. Chem. Int. Ed.* **2002**, *41*, 3677.