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Binaphthol-Catalyzed Asymmetric Conjugate Arylboration of Enones

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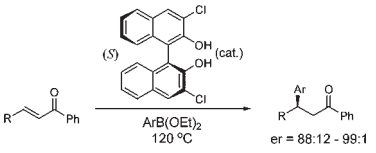
ABSTRACT



Conjugate addition of arylboronates to α,β-unsaturated ketones may be catalyzed by chiral binaphthols with enantioselectivities of up to 99:1. Best results were observed with 3,3′-dichloro-BINOL. This chemistry was applied to syntheses of intermediates for syntheses of (+)-indatraline and (+)-tolterodine.

The Rh-catalyzed asymmetric conjugate addition of alkenyl- and arylboronic acids to α,β-unsaturated carbonyl compounds, sometimes referred to as the Hayashi–Miyaura reaction, has become a very useful synthetic method since its introduction in 1998.[1−3] More recently, Pd-catalyzed asymmetric conjugate addition of arylboronic acids has emerged as an excellent method for the construction of quaternary centers.[4] The success of these reactions is due in part to the low reactivity of arylboronic acids with organic electrophiles in the absence of transition metal catalysts. We have previously exploited this low nucleophilicity of organoborons to develop asymmetric additions of alkynylboronates[5] and alkenylboronates[6] to α,β-unsaturated ketones using 3,3′-disubstituted binaphthols as catalysts. While the nature of catalysis using chiral diols is very different from that using transition metal complexes, both types of catalysts can provide products with high enantioselectivity. Since our introduction of binaphthol-catalyzed reactions of boronates, this chemistry has been extended to the allylation[7] and propargylation[8] of ketones; the allylation of *N*-acylimines;[9] the alkynylation, alkenylation, and arylation of *N*-acylimines,[10] Petasis reactions;[11] and alkenylations of acetals.[12] The conjugate alkenylboration and alkynylboration chemistry has been applied to the synthesis of natural products.[13] However, asymmetric conjugate arylation has proven to be elusive. We now report that conjugate arylborations of enones is possible and can proceed with high stereoselectivities.

Initial experiments using conditions similar to those found to be effective for alkenylborations (20 mol % ligand, CH_2Cl_2, 40 °C) were not encouraging. With enone **1a** as a test substrate and excess diethyl phenylboronate as a reagent, reactions using up to 200 mol % of various diols in

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(11) Lou, S.; Schaus, S. E. *J. Am. Chem. Soc.* **2008**, *130*, 6922–6923.

(12) Moquist, P. N.; Kodama, T.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 7096–7100.

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a variety of solvents (e.g., $ClCH_2CH_2Cl$, toluene, trifluorotoluene) at temperatures up to 120 °C for extended times consistently returned unreacted starting material with only traces of the expected product. Eventually it was found that treatment of enone **1a** with 4 equiv of diethyl phenylboronate with catalytic amounts of binaphthols *in the absence of additional solvent* provided the desired adduct.

In a screen of ligands using enone **1a**, it was found that the binaphthol had a considerable influence on the rate and enantioselectivity of the reaction (Table 1). Thus unsubstituted binaphthol **2a**, even when used in excess, gave poor conversion after 4 days at 120 °C although the enantioselectivity (er = 91:9) was quite encouraging (entry 1). Substitution at the 3- and 3′-positions with methyl groups or trifluoromethyl groups did not improve the conversion (entries 2, 3).[14] Better conversion was observed with the corresponding diphenyl-BINOL **2d** but with considerably reduced enantioselectivity (entry 4). Fortunately, diiodo-BINOL **2e** gave a reasonable level of conversion while maintaining good enantioselectivity. Further experimentation with **2e** showed that substoichiometric amounts (20 mol %) could be used with no sacrifice in conversion or selectivity (entry 5 vs 6). Increasing the reaction temperature to 140 °C increased the conversion but with a slight decrease in selectivity.

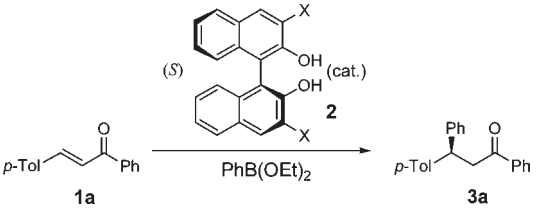
As diiodo-BINOL **2e** had provided the most encouraging results, the dibromo- and dichloro-BINOLs **2f** and **2g**, respectively, were also examined. We anticipated that more electronegative substituents would give higher reactivity. Dibromo-BINOL **2f** gave only marginally better results than the diiodo analogue, but it was gratifying to find that dichloro-BINOL **2g**[15] effected complete conversion with good selectivity (Table 1, entry 9)

Binaphthol **2g** was then used to catalyze the phenylation of a variety of enones (Table 2). For enones bearing various para-substituted phenyl groups at the β-position, consistently good enantioselectivities were observed (entries 1−4). The highest selectivities were observed with sterically demanding enones (i.e., with o-tolyl or 1-naphthyl groups) as well as a 2-furyl substituted enone. Reactions with β-alkyl enones were also successful with good selectivities observed for methyl, *n*-alkyl, and branched alkyl substituents.

Although good enantioselectivities and yields were observed for a variety of enones using dichloro-BINOL **2g** as a catalyst, reactions were sluggish, often requiring 24−72 h to go to completion. Analysis of the results presented in Table 1 suggested that a binaphthol containing relatively small electron-withdrawing groups at the 3- and 3′-positions might afford higher reactivity and still maintain a reasonable level of stereoselectivity. Thus dicyano-BINOL **2h**[16] was prepared.

Dicyano-BINOL **2h** was a much better catalyst in terms of reaction rates; for all enones examined, reactions were

Table 1. Initial Ligand Screen with Enone **1a**

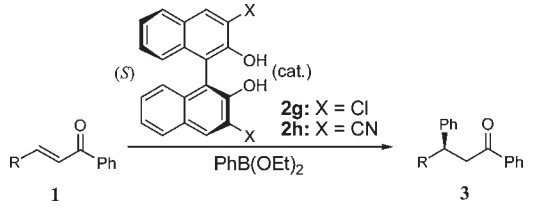


1a **3a**

entry	cat. (X)	loading (mol %)	temp (°C)/ time (h)	conv[a] (%)	er[b]
1	**2a** (H)	200	120/96	<50	91:9
2	**2b** (CH_3)	100	120/72	35	88:12
3	**2c**[c] (CF_3)	100	120/72	36	8:92
4	**2d** (Ph)	100	120/72	84	71:29
5	**2e** (I)	100	120/72	69	89:11
6	**2e** (I)	20	120/96	72	89:11
7	**2e** (I)	20	140/96	88	86:14
8	**2f**[c](Br)	50	120/72	91	8:92
9	**2g** (Cl)	20	120/72	100	91:9

[a] Conversion was determined by ^{1}H NMR analysis of crude reaction mixtures. [b] Enantiomeric ratio was determined by chiral HPLC analysis. [c] (*R*)-BINOL was used.

Table 2. Phenylboration of Enones with BINOLs **2g** and **2h**[a]



1 **3**

entry	enone (R)	prod	er[b] (% yield) with **2g**[c]	er[b] (% yield) with **2h**[c]
1	**1a** (4-$CH_3C_6H_4$)	**3a**	91:9 (90)	84:16 (97)[d]
2	**1b** (4-$CH_3OC_6H_4$)	**3b**	94:6 (66)	74:26 (68)
3	**1c** (4-ClC_6H_4)	**3c**	90:10 (74)	79:21 (75)
4	**1d** (4-BrC_6H_4)	**3d**	91:9 (80)	nd
5	**1e** (2-$CH_3C_6H_4$)	**3e**	99:1 (75)	95:5 (63)
6	**1f** (1-naphthyl)	**3f**	98:2 (86)	97:3 (90)
7	**1g** (CH_3)	**3g**	93:7 (66)	85:15 (85)
8	**1h** (*n*-C_4H_9)	**3h**	90:10 (72)	86:14 (61)
9	**1i** (*i*-C_3H_7)	**3i**	90:10 (83)	86:14 (86)
10	**1j** (2-furyl)	**3j**	99:1 (65)	nd

[a] Reactions were carried out at 120 °C for 24−72 h with 20 mol % **2g** and 4 equiv of $PhB(OEt)_2$ or for 5 h with 20 mol % **2h**. [b] Enantiomeric ratio was determined by chiral HPLC analysis. [c] Isolated yields after flash chromatography. [d] Reaction was run at 100 °C for 72 h.

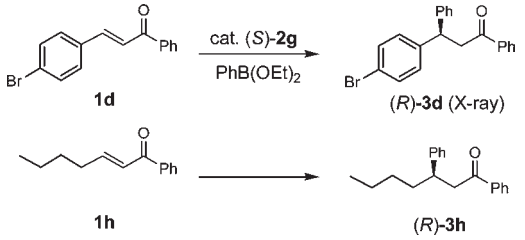
(14) The use of modified BINOLs in asymmetric synthesis has been reviewed: Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155–3211.

(15) BINOL **2g** (or its enantiomer) has been used in (a) aldol reactions: Orito, Y.; Hashimoto, S.; Ishizuka, T.; Nakajima, M. *Tetrahedron* **2006**, *62*, 390–400. Ichibakas, T.; Orito, Y.; Nakajima, M. *Tetrahedron Lett.* **2008**, *49*, 4427–4429. (b) Allylations: Wallner, O. A.; Olsson, V. J.; Eriksson, L.; Szabó, K. J. *Inorg. Chim. Acta* **2006**, *359*, 1767–1772. (c) Alkynylations: Ueda, T.; Tanaka, K.; Ichibakase, T.; Orito, Y.; Nakajima, M. *Tetrahedron* **2010**, *66*, 7726–7731. (d) Strecker reactions: Kobayashi, S.; Ishitani, H. *Chirality* **2000**, *12*, 540–543.

complete within 5 h at 120 °C. This higher reactivity allowed the reaction to be run at lower temperatures (Table 2, entry 1), but unfortunately, enantioselectivities were consistently lower than those observed with dichloro-BINOL **2g**.

To determine the absolute configuration of the adducts, an X-ray structure was determined for the major isomer formed upon phenylation of bromoenone **1d** (Scheme 1). Using (*S*)-**2g** as the catalyst, the major product formed from **1d** was (*R*)-**3d**. Similarly, phenylation of enone **1h** provided known (*R*)-**3h** as the major product.[17] For the other adducts, the absolute configurations were assigned by inference.

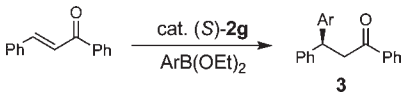
Scheme 1. Determination of Absolute Configurations



Substituted phenylboronates were also examined (Table 3).[18] These reactions afforded results very similar to those observed with diethyl phenylboronate in that the expected conjugate addition products were formed in good yields with high selectivities. Using chalcone (**1**, R = Ph) as the substrate and (*S*)-**2g** as the catalyst, the major products formed were enantiomeric with those formed by addition of diethyl phenylboronate to substituted chalcones using the same catalyst (Table 2). Thus products **3a**–**e** in Table 3 have an (*S*)-configuration while the same products in Table 2 have an (*R*)-configuration. In other words, by suitable choice of substrate and reagent, one can prepare either enantiomer of various β,β-diaryl ketones using the same catalyst. This may be experimentally convenient if only one enantiomer of the catalyst were on hand. Alternatively, the enantiomeric catalyst could be used to prepare the enantiomeric adduct.

The utility of this asymmetric conjugate arylation was demonstrated by the preparation of an intermediate in previous syntheses of (+)-indatraline (Scheme 2).[19,20] (+)-Indatraline is a monoamine uptake inhibitor that has been

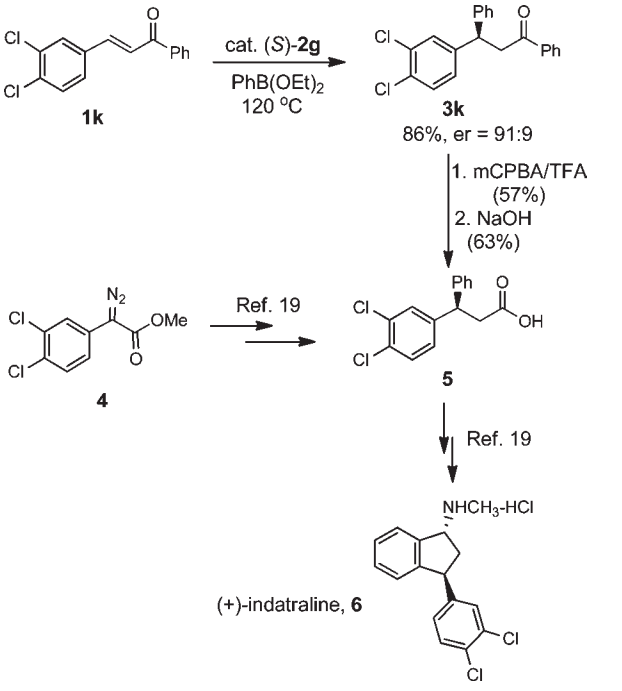
Table 3. Arylboration of Chalcone with BINOL **2g**[a]



entry	Ar	time (h)	prod	yield[b]	er[c]
1	4-$CH_3C_6H_4$	20	**3a**	84	93:7
2	4-$CH_3OC_6H_4$	29	**3b**	88	89:11
3	4-ClC_6H_4	46	**3c**	67[d]	91:9
4	2-$CH_3C_6H_4$	48	**3e**	70	95:5

[a] Reactions were carried out at 120 °C for 20–48 h with 20 mol % **2g** and 4 equiv of $ArB(OEt)_2$. [c] Enantiomeric ratio was determined by chiral HPLC analysis. [b] Isolated yields after flash chromatography. [d] Conversion was only 75% by ^1H NMR analysis after 48 h.

Scheme 2. Synthesis of a (+)-Indatraline Intermediate



shown to block reuptake of dopamine, norepinephrine, and serotonin. While there are many approaches to (+)-**6** using resolution techniques, there are relatively few asymmetric syntheses. In the first asymmetric synthesis of (+)-**6**, diazoester **4** was converted to acid **5** in six steps using a Rh-catalyzed C–H insertion as the key reaction.[19] Subsequently, **5** has been prepared using Cu-catalyzed asymmetric conjugate reduction as the key step.[20,21] In our approach, conjugate phenylation of enone **1k** provided ketone **3k** in good yield (86%) and selectivity (er = 91:9).

(16) Previous syntheses of this diol are known, but we chose to make it by cyanation of the di-MOM ether of **2e** (CuCN/DMF) followed by deprotection.

(17) Adduct **3h** had previously been prepared by enantioselective conjugate alkylation of chalcone. The (*S*)-enantiomer elutes first on a Chiralcel OD column: Huttenloch, O.; Spieler, J.; Waldmann, H. *Chem.—Eur. J.* **2001**, *7*, 671–675.

(18) A wide variety of substituted phenylboronic acids are commercially available. These were readily converted into boronates by esterification with ethanol ($CHCl_3$, Dean–Stark, molecular sieves).

(19) Davies, H. M. L.; Gregg, T. M. *Tetrahedron Lett.* **2002**, *43*, 4951–4953.

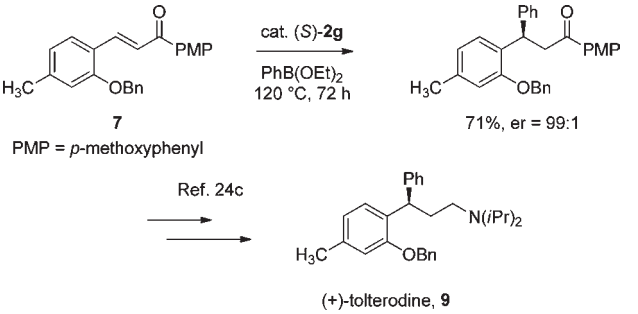
(20) Yoo, K.; Kim, H.; Yun, J. *Chem.—Eur. J.* **2009**, *15*, 11134–11138.

(21) Very recently, a synthesis involving Rh-catalyzed phenylboration of a *tert*-butyl enone has appeared: Wei, W.-T.; Yeh, J.-Y.; Kuo, T.-S.; Wu, H.-L. *Chem.—Eur. J.* **2011**, *17*, 11405–11409.

Ketone **3k** proved to be resistant to Baeyer–Villiger oxidation using mCPBA giving only partial conversion even after extended times with excess reagent. The low reactivity of phenyl ketones toward BV oxidation using mCPBA has been previously observed by others who were able to achieve good conversions using anhydrous CF_3CO_3H.[22] We chose to use an experimentally more convenient procedure involving mCPBA with TFA[23] which smoothly provided the expected phenyl ester. Hydrolysis (NaOH) then gave acid **5**.

This chemistry has also been applied to the synthesis of an intermediate previously used in an approach to (+)-tolterodine (DETROL), a muscarine receptor antagonist (Scheme 3). (+)-Tolterodine has been the target of many synthetic approaches as a showcase for methods to prepare diaryl substituted stereogenic centers.[24] (+)-Tolterodine was particularly attractive for our approach as one of the aryl rings bears an *ortho*-substituent, which was expected to give very high selectivity in the conjugate addition (as observed for enone **1e**). In practice, it was gratifying to find that phenylboration of **7** provided the expected adduct **8** with er = 99:1. Ketone **8** has previously been converted (by Baeyer–Villiger oxidation, hydrolysis, amide formation, and then reduction) into (+)-tolterodine **9**.[24c]

Scheme 3. Synthesis of a (+)-Tolterodine Intermediate



In summary, we have shown that asymmetric conjugate arylations may be carried out using chiral binaphthols as catalysts. Reactions are relatively sluggish but proceed at synthetically useful rates with diols containing electron-withdrawing groups. The best results were observed with dichloro-BINOL **2g**. High selectivities and yields may be obtained, and the products may be useful for the synthesis of enantioenriched compounds. Efforts to develop more reactive systems are underway.

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Supporting Information Available. Experimental procedures and spectral data for compounds **2g**, **2h**, **3a**–**3k**, **5**, and **8**, and X-ray data for compound (*R*)-**3d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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