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Nickel-BINAP Catalyzed Enantioselective α-Arylation of α-Substituted γ-Butyrolactones

Dirk J. Spielvogel and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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Recently, the Pd-catalyzed α-arylation of ketones and related compounds has received a great deal of attention. A number of Pd(0)-based systems have been reported that are useful for intra- and intermolecular versions of this process.[1] The enantioselective construction of quaternary centers by α-arylation/vinylation methodology has also been detailed.[1c,2]

Herein, we disclose that a Ni(0)−BINAP system can be used for the highly enantioselective α-arylation of α-substituted γ-butyrolactones with aryl chlorides and bromides. We also report an accelerating effect caused by the addition of zinc(II) salts. Initial experiments, using conditions similar to those employed in Pd(0)-based procedures,[2a] focused on the coupling of α-methyl-γ-butyrolactone **1a** and 2-bromonaphthalene with NaO*t*-Bu as base. Unfortunately, this protocol resulted primarily in reduction of the aryl bromide. Upon changing the base from NaO*t*-Bu to NaHMDS, the efficient formation of product was realized. After some experimentation, we found that the Pd-catalyzed arylation proceeded with moderate yield and enantioselectivity. Substitution of Pd(0) with Ni(0) proved to be instrumental for the production of highly enantiomerically enriched products.[3] Thus, using 5 mol % Ni[(*S*)-BINAP](COD), prepared *in situ* from $Ni(COD)_2$, provided the arylation products with high ee values, albeit in low yields (Table 1, entries 1 and 3). The increase in enantioselectivity may be due to a greater stereochemical communication between ligand and substrate(s) that results from the smaller Ni-center. Aryl chlorides can be utilized with comparable reaction rates, less reduction, and minimally lower enantioselectivities compared to aryl bromides (entry 4); no anisole is detected in the reactions to yield (-)-**3** (entry 4). Furthermore, at low conversions (-)-**3** is formed quantitatively. Attempts to accelerate the reaction by increasing the quantity of catalyst to 10 mol % were marginally successful (entry 5).

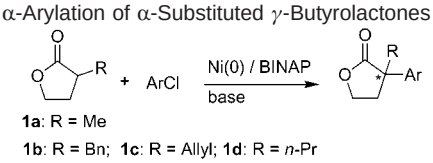
To facilitate the experimental procedure we envisioned the *in situ* zinc reduction of $(BINAP)NiBr_2$. To probe the effect of the salt that would be formed, 15 mol % of $ZnBr_2$ was added as a THF solution to the reaction mixture as previously prepared (entry 4). Pleasingly, a dramatic increase in both the rate of the reaction and the isolated yield of the product was observed (entries 2 and 6).

With this method, a variety of electron-rich and electron-poor aryl halides with meta or para substituents can be successfully coupled with excellent enantioselectivities (90−97%). The yields differ due to the extent of reduction of the aryl halide. The reaction conditions allow for the presence of ethyl esters and silyl ethers (Table 1, entries 10 and 13). Unfortunately, ortho-substituted aryl halides gave none of the desired product.

To determine the absolute stereochemistry of (-)-**2**, we sought to convert the lactone by treatment with 4-iodoaniline to the corresponding anilide. Surprisingly, reaction under Weinreb's conditions yielded lactam (-)-**11**.[4] X-ray analysis of (-)-**11** revealed the absolute stereochemistry to be (*S*) as shown in Scheme 3.[5] Notably, the sense of induction observed with the Ni(*S*)-(BINAP)

* Address correspondence to this author. E-mail: sbuchwal@mit.edu.

Scheme 1 α-Arylation of α-Substituted γ-Butyrolactones



Scheme 2. Palladium-Catalyzed α-Arylation of **1a**

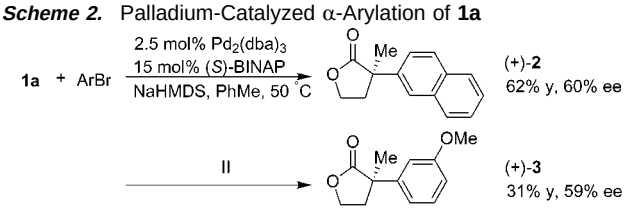


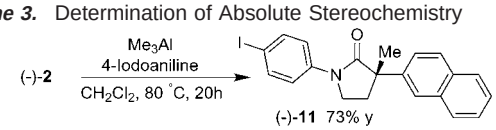
Table 1. Nickel-Catalyzed α-Arylation of **1a**[a]

Entry	ArX	Product	Yield (%)[b]	ee (%)[c]	ArH (%)[d]
1[e]	ArBr	(-)-(*S*)-**2**	33[d]	98	45
2	ArCl		95	94	< 10
3[e]	ArBr	(-)-**3**	29[d]	99	< 10
4[e]	ArCl		40[d]	95	0
5[e,f]	ArCl		52[d]	95	0
6	ArCl		86	96	0
7[g]	ArCl	(-)-**4**	76	94	0
8	ArCl	(-)-**5**	86	> 97	n.d.
9	ArCl	(-)-**6**	81	> 97	n.d.
10	ArCl	(-)-**7**	67	95	n.d.
11	ArBr	(-)-**8**	57	94	28
12	ArBr	(-)-**9**	58	93	n.d.
13[h]	ArCl	(-)-**10**	73	90	n.d.

[a] Conditions: 5 mol % of $Ni(COD)_2$, 8.5 mol % of (*S*)-BINAP, 2 equiv of **1a**, 2.3 equiv of NaHMDS, 15 mol % of $ZnBr_2$, 1 equiv of ArX (0.25 mmol), 0.75 mL of toluene, 0.25 mL of THF, 17−20 h, 60 °C. [b] Isolated yield. [c] Determined by HPLC. [d] GC yield. [e] 0 mol % of $ZnBr_2$, 1 mL of toluene. [f] 10 mol % of $Ni(COD)_2$, 17 mol % of (*S*)-BINAP. [g] 80 °C. [h] 1 mmol of ArCl, 2 mmol of **1a**, 2 mmol of NaHMDS.

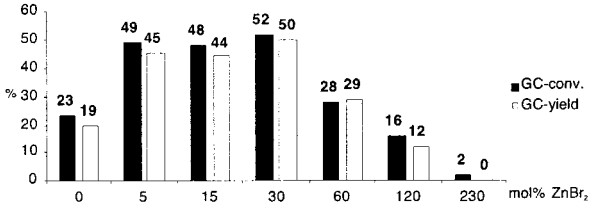
10.1021/ja017545t CCC: $22.00

Scheme 3. Determination of Absolute Stereochemistry



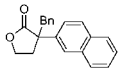
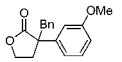
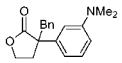
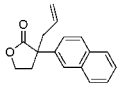
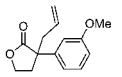
[a] Conditions: 10 mol % of $Ni(COD)_2$, 17 mol % of (*S*)-BINAP, 2 equiv of lactone, 2.3 equiv of NaHMDS, 15 mol % of $ZnBr_2$, 1 equiv of ArCl (0.25 mmol), 0.75 mL of toluene, 0.25 mL of THF, 17−20 h. [b] Isolated yield. [c] Determined by HPLC. [d] GC yield. [e] 5 mol % of $Ni(COD)_2$, 8.5 mol % of (*S*)-BINAP. [f] 0.5 mmol of **1c**, 0.575 mmol of NaHMDS, 0.75 mmol of ArCl.

Chart 1. Influence of Zn(II) Stoichiometry[a]



[a] Conditions: 5 mol % $Ni(COD)_2$, 8.5 mol % (*S*)-BINAP, 2 equiv of **1a**, 2.3 equiv of NaHMDS, $ZnBr_2$, 1 equiv of 3-chloroanisole (0.25 mmol), 0.75 mL of toluene, 0.25 mL of THF, 3 h, 60 °C.

Table 2. Nickel-Catalyzed α-Arylation of **1b**, **1c**, and **1d**[a]

Entry	Lactone	Product	Temp. (°C)	Yield (%)[b]	ee (%)[c]	ArH (%)[d]
1[e]	**1b**		60	91	96	< 5
2	**1b**		80	63	94	0
3	**1b**		80	58	96	n.d.
4[e]	**1c**		60	80	89	< 10
5	**1c**		60	56	95	0
6[f]	**1c**		60	25	83	n.d.
7[e]	**1d**		60	84	98	n.d.

system in the formation of **2** and **3** was opposite to that observed with Pd(*S*)-(BINAP) (see Scheme 2 and Table 1, entries 1 and 3).

To gain further insight into the accelerating effect of $ZnBr_2$ in the reaction of **1a** with 3-chloroanisole, the process was examined with use of different Zn(II) salts[6] and with varying concentrations of $ZnBr_2$ (see Chart 1). Comparable accelerating effects are observed with $ZnBr_2$, $ZnCl_2$, $Zn(OTf)_2$, and $Zn(O\textit{t}\text{-}Bu)_2$. Strongly ionic (ZnF_2)[7] and more covalent (ZnI_2)[7] additives show no influence.[8] The enantioselectivity is independent of the zinc(II) salt employed. Variation of the $[ZnBr_2]$ reveals an accelerating effect at catalytic quantities (5−30 mol %) and an inhibiting effect at stoichiometric quantities (>120 mol %).

On the basis of these results and those described by others,[9] it seems reasonable that $ZnBr_2$ acts as a Lewis acid that facilitates bromide abstraction from (BINAP)Ni(Ar)(Br) to form a cationic $[(BINAP)Ni(Ar)]^+$ species that subsequently undergoes transmetalation more rapidly. The inhibition observed with stoichiometric Zn(II) may be due to the formation of a less reactive zinc enolate.[10,11] This is in agreement with the finding that reactions employing 1 equiv of the Na-enolate of **1a** provide similar yields as reactions with 2 equiv of Na-enolate to which 1 equiv of $ZnBr_2$ was added.

To further examine the scope of the enantioselective lactone arylation, the reactions with α-benzyl- (**1b**), α-allyl- (**1c**), and α-propyl-γ-butyrolactone (**1d**) were investigated. The arylation of **1b**−**d** proceeded with good enantioselectivities (83−96%). The system is, however, sensitive to the size of the α-substituent. Thus, longer reaction times or higher reaction temperatures were necessary with **1b**−**c**, resulting in lower yields (Table 2, entries 2, 3, and 5). The terminal olefin moiety of **1c** also lends itself to side reaction(s), thus decreasing the isolated yield of the desired product (entries 4−6).[12]

In summary, the application of a Ni(BINAP) system for the α-arylation of α-substituted γ-butyrolactones has been described. Coupled with an accelerating effect of Zn(II) salts, α-quaternization is achieved with high enantioselectivities and moderate to excellent yields. Future work will focus on expanding the scope of this enantioselective arylation system. Elucidation of the exact role of Zn(II) as well as investigations into the stereochemical complementarity of Pd(*S*)-BINAP and Ni(*S*)-BINAP are in progress.

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

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(5) Configurations of (−)-**3**−(−)-**13** are assigned by analogy to (−)-(*S*)-**2**.

(6) For Chart 2 see Supporting Information.

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(8) The use of THF as a cosolvent is necessary to observe the $ZnBr_2$-based rate acceleration. Both ZnF_2 and $Zn(OTf)_2$ show poor solubility in THF and toluene. Addition of 15 mol % $ZnBr_2$ to the Pd-catalyzed reaction of **1a** with 3-bromoanisole (2.5 mol % $Pd_2(dba)_3$, 9 mol % (*S*)-BINAP) also leads to an improved yield ((+)-**3**: y = 58%, ee = 54%).

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(12) ^{1}H NMR and mass spectra analysis of the crude reaction mixture suggest the formation of small amounts of Heck reaction products.

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