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Synthesis of Tetra-ortho-substituted, Phosphorus-Containing and Carbonyl-Containing Biaryls Utilizing a Diels−Alder Approach

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Abstract: The application of the Diels−Alder approach to biaryls (DAB) is described for the synthesis of tetra-ortho-substituted biaryl compounds containing orthogonally functionalized substituents. The syntheses of phosphorus-containing, disubstituted alkynes and carbonyl-containing, disubstituted alkynes were accomplished in two to three steps from commercially available reagents. Subsequent Diels−Alder cycloadditions with a range of oxygenated dienes yielded the target biaryls. Further functionalization through palladium-couplings is demonstrated on the phosphorus-containing biaryls. In addition, selective manipulation of each of the remaining ortho substituents on the phosphorus-containing biaryls is demonstrated. One of these phosphorus-containing derivatives is utilized as a highly active catalyst for Suzuki coupling. For the carbonyl-containing series, a wide range of dienophile substituents were screened including esters, ketones, and amides. The key Diels−Alder cycloadditions proceeded smoothly with the commercially available 1-methoxy-1,3-cyclohexadiene to yield the resultant tetra-ortho-substituted biaryls with excellent regioselectivity. The scope of the cycloaddition process was also explored on the carbonyl-containing dienophiles with a series of cyclic dienes. Acyclic dienes were also screened; however, they did not prove effective in the Diels−Alder process with the carbonyl-containing acetylenes. The ability to isolate enantiomerically pure biaryl atropisomers using a benzyl oxazolidinone is disclosed. Finally, the subsequent conversion to an axially chiral anilino alcohol is also reported.

Introduction

The synthesis via the aryl−aryl σ linkage of highly substituted biaryl compounds, particularly structures containing four ortho substituents, has generated considerable synthetic attention—primarily through the use of various transition metal-mediated methods to form the linking σ bond.[1−3] This task has long been considered one of the premier challenges in the construction of complex polyaromatic systems.[4] An alternative approach to their construction has been reported by our laboratory[5] and others[6] involving a Diels−Alder reaction of suitably functionalized, disubstituted acetylenes. In this paper, we disclose a full account of our work utilizing phosphorus-containing and carbonyl-containing disubstituted aryl acetylenes.

Results and Discussion

Phosphorus-Containing Chloro Series. Our initial forays into this field started from the alkyne,[7] available in one step from the commercially available 2-chloro-6-nitro-benzaldehyde using the Ohira−Bestmann reagent[8] (K_2CO_3, MeOH, 96%) (Scheme 1). After some experimentation, we discovered that use of lithium diispropylamide (LDA) followed by addition of 0.8 equiv of the requisite phosphorus electrophile [$Ph_2P(O)Cl$ or $(EtO)_2P(O)Cl$] gave excellent yields of the disubstituted acetylenes **2a** and **2b**. Use of alternate bases (*n*-BuLi, NaH, KHMDS, LiHMDS, TBAF, *i*-PrMgCl) led to only trace amounts of the desired product. We are not certain at this time why LDA is uniquely capable in the deprotontation of these terminal alkynes. Next, we embarked on the crucial Diels−Alder process. We hypothesized that that the Brassard diene **3**[9] would be well-

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(1) For a recent review of the area, see: Wallace, T. W. *Org. Biomol. Chem.* **2006**, *4*, 3197−210.
(2) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 1−241.
(3) For alternative methods, See: Nishida, G.; Suzuki, N.; Noguchi, K.; Tanaka, K. *Org. Lett.* **2006**, *8*, 3489−3492.
(4) (a) Montoya-Pelaez, P. J.; Uh, Y.-S.; Lata, C.; Thompson, M. P.; Lemieux, R. P.; Crudden, C. M. *J. Org. Chem.* **2006**, *71*, 5921−5929. (b) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028−13032.
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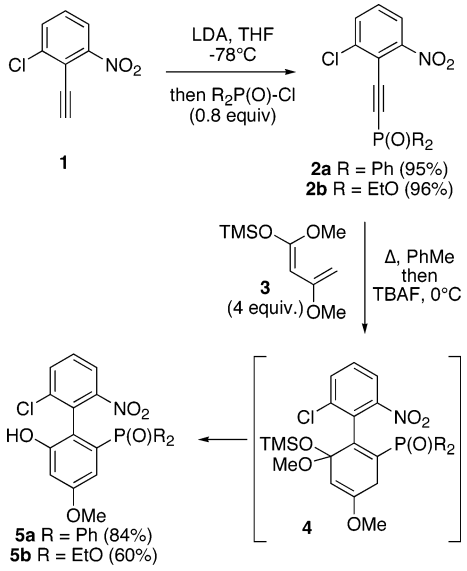
(6) (a) Knolker, H.-J.; Baum, E.; Hopfmann, T. *Tetrahedron Lett.* **1995**, *36*, 5339−42. (b) Bateson, J. H.; Smith, C. F.; Wilkinson, J. B. *J. Chem. Soc. Perkin Trans. I* **1991**, 651−653. (c) Kanakam, C. C.; Mani, N. S.; Ramanathan, H.; Subba Rao, G. S. R. *J. Chem. Soc., Perkin Trans. I* **1989**, 1907−1913. (d) Liu, Y.; Lu, K.; Dai, M.; Wang, K.; Wu, W.; Chen, J.; Quan, J.; Yang, Z. *Org. Lett.* **2007**, *9*, 805−808.
(7) (a) Naffziger, M. R.; Ashburn, B. O.; Perkins, J. R.; Carter, R. G. *J. Org. Chem.*, published online June 29, 2007 http://dx.doi.org/10.1021/jo070740r. For additional use of the 2-chloro-6-nitro-phenylacetylene (**1**), see: (b) Ashburn, B. O.; Carter, R. G. *J. Org. Chem.*, published online June 29, 2007 http://dx.doi.org/10.1021/jo070812e.
(8) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561−564. (b) S. Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, J. *SYNLETT* **1996**, 521−522. For preparation of **6**, see also: (c) Goundry, W. R. F.; Baldwin, J. E.; Lee, V. *Tetrehedron* **2003**, *59*, 1719−1729. (d) Kitamura, M.; Tokynaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2931−2932.
(9) Savard, J.; Brassard, P. *Tetrahedron* **1984**, *40*, 3455−3464.

Scheme 1. Synthesis of First-Generation Phosphorus-Containing Biaryls



suited for this transformation. Gratifyingly, the Diels−Alder process proceeded quite cleanly via the intermediate **4**. This intermediate was not isolated (as it proved quite unstable), and in situ cleavage of the silyl ether **4** to induce aromatization was accomplished with TBAF to yield the biaryls **5a** and **5b** in good yield (60−84%). Conclusive structural assignment of biaryl **5b** was obtained via X-ray crystallographic analysis (Figure 1).

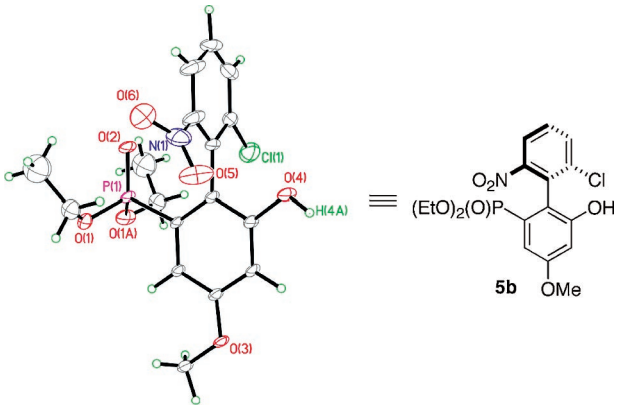
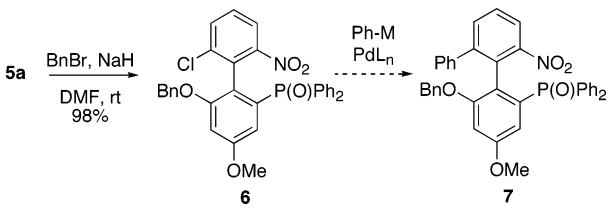


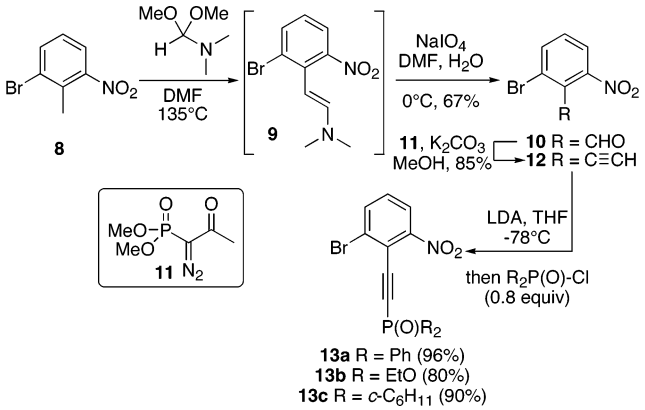
Figure 1. ORTEP representation of the X-ray structure of biaryl **5b**.

Next, we explored the potential palladium-coupling of the aryl chloride (Scheme 2). Despite our considerable efforts with a wide range of catalyst systems,[10−12] we were unable to effect C−Cl insertion on biaryl **6**. Two possible explanations can be offered for this lack of reactivity: the increased steric requirement of the four ortho substituent or the disruptive coordinating ability of the phosphine-oxide.

Scheme 2. Attempted Palladium-Coupling of Chlorinated Phosphorus-Containing Biaryls



Scheme 3. Synthesis of Brominated, Phosphorus-Containing Dienophiles



Phosphorus-Containing Bromo Series. On the basis of the inability to couple the C−Cl bond, the logical solution that we chose to employ was to substitute a more reactive halogen substituent. Consequently, the bromo-acetylene **12** needed to be synthesized (Scheme 3). While the 2-bromo-6-nitro-benzaldehyde **10** was known, its preparation required a tedious three-step protocol.[13] We instead chose to exploit chemistry first reported by scientists at Pfizer involving the dimethyl acetal of DMF followed by cleavage of the resultant enamine with $NaIO_4$.[7,14] Unfortunately, use of the identical reaction conditions on the 2-bromo-6-nitro-toluene (**8**) did not cleanly generate the desired aldehyde **10**. We did discover, however, that if the conditions were modified by cooling of the intermediate enamine **9** solution to 0 °C and by rapidly adding it to a vigorously stirred solution of $NaIO_4$ at 0 °C, the undesired impurities were completely suppressed.[15] This one-pot protocol does not require the isolation of the intermediate enamine **9** and has proven quite effective in our hands. Subsequent alkyne formation with the Ohira−Bestmann reagent **11**[8] provided **12**. Again, deprotonation with LDA followed by addition of the phosphorus electrophile [$Ph_2P(O)Cl$, $(c\text{-}C_6H_{11})_2P(O)Cl$, or $(EtO)_2P(O)Cl$] gave the desired disubstituted alkynes **13a**−**c**.

We were gratified to observe that the Diels−Alder reactions again proceeded well (Scheme 4). We were able to employ a range of dienes **15**, **17**, and **19** in addition to the Brassard diene **3**. The generality of this approach clearly demonstrates the unique power of the Diels−Alder reaction to construct even the most congested of biaryl linkages. X-ray crystal structures of biaryls **14a** and **14c** were determined—further confirming the regiochemical outcome of the Diels−Alder process. Interest-

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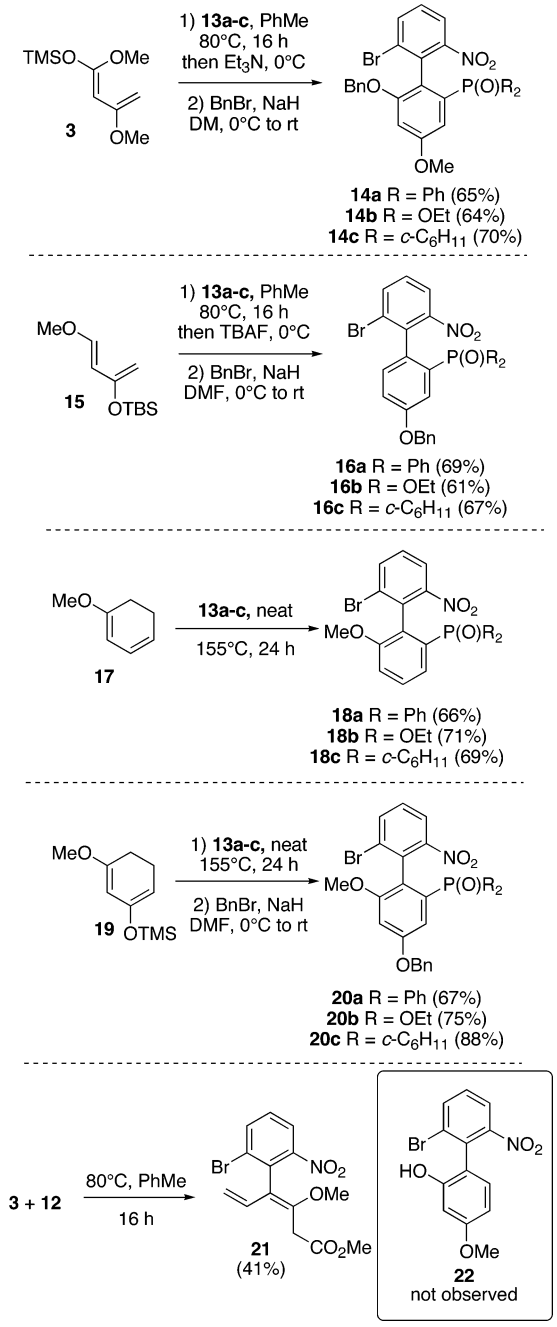
(13) Li, J.-S.; Fan, Y.-H.; Zhang, Y.; Marky, L. A.; Gold, B. *J. Am. Chem. Soc.* **2003**, *125*, 2084−2093.
(14) (a) Vetlino, M. G.; Coe, J. W. *Tetrahedron Lett.* **1994**, *35*, 219−222. (b) Caron, S.; Vazquez, E.; Stevens, R. W.; Nahao, K.; Koike, H.; Murata, Y. *J. Org. Chem.* **2003**, *68*, 4104−4107.
(15) Primarily, we observed the homologated aldehyde resulting from the hydrolysis of the enamine intermediate as the predominate impurity.

Scheme 4. Synthesis of Second-Generation Phosphorus-Containing Biaryls



ingly, Diels−Alder reaction of the monosubstituted alkyne **12** with Brassard diene **3** generates none of the expected biaryl adduct **22**; instead the enol ether **21** is formed in reasonable yield (41%). This product was not observed with the 2-chloro version but with the 3-chloro variant,[7] thus demonstrating the unique role that the halogen plays in the Diels−Alder process.

We next sought to demonstrate the feasibility of accomplishing metal-mediated coupling on the resultant biaryls. The pentasubstituted biaryls **14a**−**c** were chosen for initial screening (Table 1). We explored a range of Suzuki, Stille, and Negishi conditions for accomplishing this transformation—including Buchwald's ligands,[12] P(*c*-C_6H_{11})$_3$/Pd_2(dba)$_3$,[11] Pd(dppf)Cl_2, and Pd(OAc)$_2$/dppp.[16] We were pleased to find that the (*t*-Bu_3P)$_2$-

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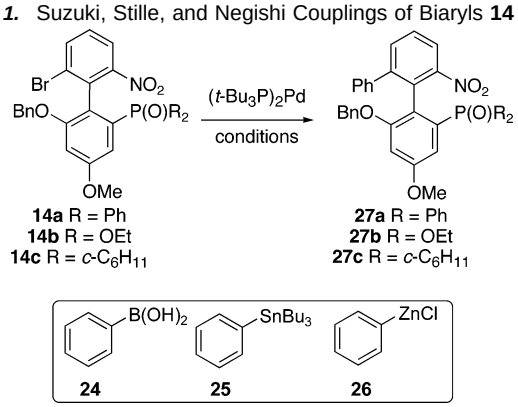
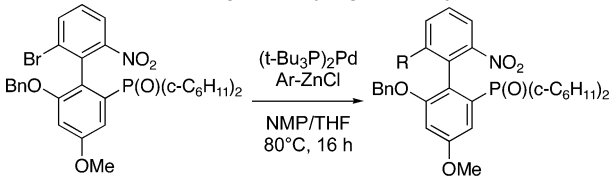
Table 1. Suzuki, Stille, and Negishi Couplings of Biaryls **14**



R	Suzuki[a] yield (%)	Stille[b] yield (%)	Negishi[c] yield (%)
Ph	61	60	59
c-C_6H_{11}	72	66	62
EtO	63	60	57

[a] Catalyst (20 mol %), **23** (3 equiv), KF (9 equiv), NMP, 100 °C, 16 h. [b] Catalyst (20 mol %), **24** (3 equiv), CsF (9 equiv), NMP, 60 °C, 16 h. [c] Catalyst (10 mol %), **25** (1.5 equiv), NMP/THF, 80 °C, 16 h.

Table 2. Variation of Negishi Couplings on Biaryl **14c**



entry	Ar–ZnCl[a]	yield (%)
a	4-methoxyphenylzinc chloride	59
b	3-methoxyphenylzinc chloride	58
c	2-methoxyphenylzinc chloride	0
d	2-methylphenylzinc chloride	61
e	2,6-dimethylphenylzinc chloride[b]	66
f	pentafluorophenylzinc chloride	57

[a] Organozinc species was formed by addition of the in situ generated organomagnesium species to a 1 M THF solution of anhydrous zinc chloride. [b] Extended reaction time (48 h) was employed for this coupling.

Pd° system developed by the Fu laboratory gave positive results in the coupling processes.[10] We found that efficient Suzuki and Stille couplings could be accomplished with the corresponding phenyl boronic acid (**24**) and the tributylphenyl stannane (**25**). These couplings, however, required high catalyst loading (20 mol %) and excess aryl metallo species (3 equiv) to proceed to completion. In addition, we found very poor functional group tolerance with substituted aryl boronic acids or aryl stannane—routinely resulting in incomplete reaction and low chemical yields. In contrast, we found that the organozinc species coupled quite efficiently with reduced catalyst loading (10 mol %) and phenylzinc chloride (**26**, 1.5 equiv).

It became clear that the Negishi conditions provided the largest opportunity of substrate scope (Table 2). The dicyclohexylphosphine oxide biaryl was selected for further exploration. Good tolerance for substitution on the aryl ring was observed with substitution in the ortho, meta, or para positions. One exception to this observation is the failure of 2-methoxyphenyl zinc chloride to undergo successful coupling. The problem appears to be electronic in nature as additional steric substitution

Scheme 5. Further Functional Modification of Biaryls

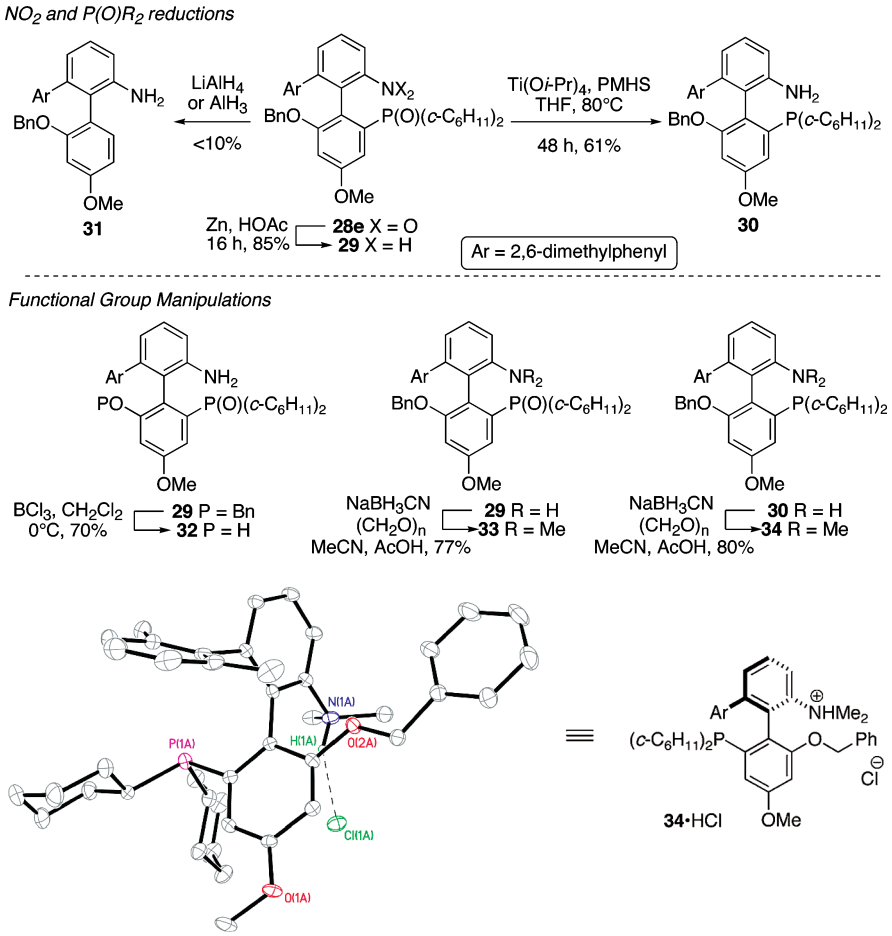


Figure 2. ORTEP representation of the X-ray structure for biaryl **34**·HCl.

ortho to the organozinc species does not disrupt the palladium coupling (entries d and e). In fact, the 2,6-dimethylphenyl zinc chloride proved the most efficient substrate for this coupling process. It should also be noted that electron-withdrawing substituents are tolerated (entry f). The structures of compounds **28a**, **28e**, and **28f** were confirmed by single-crystal X-ray diffraction methods.

Further functionalization of the biaryl moiety was also possible (Scheme 5). The nitro group can be easily reduced using zinc in acetic acid (85%). Attempted hydrogenation of the nitro compound **28e** to the amino compound **29** gave complex mixtures and low mass recovery [presumably due to irreversible binding of the resultant phosphine-oxide amino alcohol (e.g., **32**) to the metal surface]. A wide range of conditions were screened for the reduction of the phosphine oxide moiety. The most common set of conditions typically used for this transformation employs $HSiCl_3$ and Et_3N;[17] however, these conditions provided none of the desired phosphine; only extensive decomposition was observed. We also screened several aluminum-based reagents (e.g., LAH, AlH_3) which again provided none of the desired product. Instead, a small amount of the tri-ortho-substituted biaryl **31** was isolated with selective C−P bond cleavage. Fortunately, the desired reduction of the P−O bond could be accomplished using conditions developed by Lawrence and co-workers.[18] Further manipulation of the functional groups on the biaryls was possible. The benzyl ether could be readily cleaved with BCl_3 to provide the phenol **32** in good yield. Also, the anilino group present in compounds **29** and **30** could be reductively aminated using $NaBH_3CN$ and paraformaldehyde to give the dimethylamino compounds **33** and **34**. X-ray crystallographic analysis of the hydrochloride salt of the dimethylamino phosphine **34** is shown in Figure 2. Also, attempted reduction of the phosphine oxide moiety in biaryl **33** (using the Lawrence conditions) gave low yield of the product **34** (38%) with a significant amount of recovered starting material.

The dimethylamino phosphine **34** was screened for its potential utility as a ligand in palladium-mediated processes (Scheme 6). We were pleased to observe that it serves as a highly active ligand for cross-coupling reactions. The synthesized ligand **34** appears to be critical to the success for these transformations as the experiment in the absence of phosphine with boronic acid **35** and bromide **36** [5 mol % $Pd(OAc)_2$, K_3PO_4, PhMe, 100 °C, 20 h] gave only a small amount (18%) of the desired coupled material **37**. The use of alternate phosphines (e.g., PPh_3) as a substitute ligand also gave inferior results. It is significant to note that phosphine **34** is the sole compound we have screened to date in this process, and yet it is already

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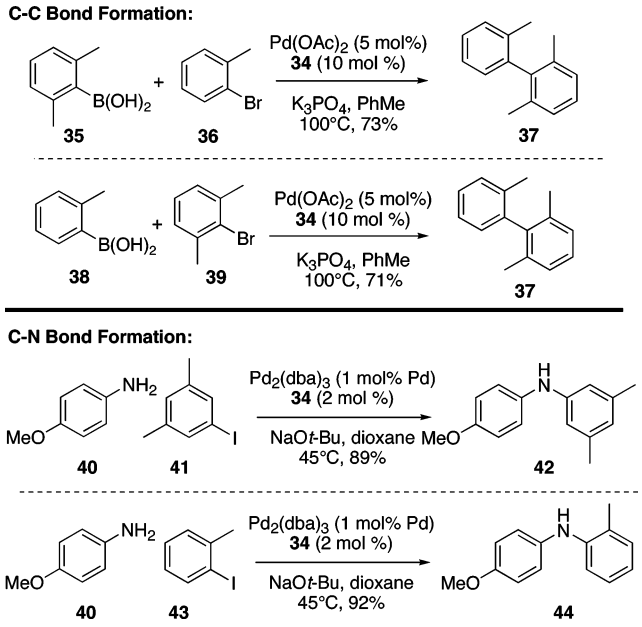
(18) Coumbe, T.; Lawrence, N. J.; Muhammad, F. *Tetrahedron Lett.* **1994**, *35*, 625−628.

Scheme 6. Utility of Ligand **34** in Cross-Coupling Reactions



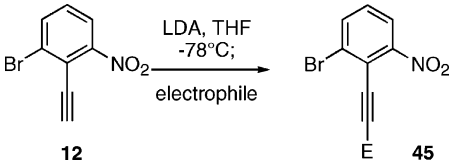
able to perform comparably with the Buchwald's *N*,*N*-dimethylamino biaryl system[19] in side-by-side experiments. We have also demonstrated that ligand **34** can be utilized for carbon–nitrogen bond formation. *p*-Anisidine (**40**) was cleanly coupled with aryl iodides **41** and **43** to generate the disubstituted anilines **42** and **44** in excellent yields.[20] Of note is the low ligand loading (2 mol %) required to facilitate this transformation.

Carbonyl-Containing Series. Given the success of the phosphorus-containing series to generate sterically congested biaryls, we sought to explore in more detail the scope of electron-withdrawing groups tolerated on the acetylene—including the possibility that the regiochemistry could be altered by the selection of alternate groups on the alkyne. In particular, we were interested in studying the effects of carbonyl moieties as their added electron-withdrawing ability might perturb the regiochemical outcome of the cycloaddition. The synthesis of these compounds could be readily accomplished from the previously mentioned alkyne **12**. Treatment of the acetylene **12** with LDA followed by the addition of the various chloroformates, carbamyl chlorides, and acid chlorides yielded the acetylenic carbonyl adducts **45a**–**l**. We are able to construct esters (entries a–c), ketones (entries d–g), and amides (entries h–i) via this approach. In addition, we prepared the menthol ester **45k** and the benzyl oxazolidinone **45l** via analogous methods. The yields were generally good to excellent. One limitation appears to be that strongly electron-withdrawing acyl chlorides give low yields due to overaddition and other uncharacterized impurities (entries f and g).

With the dienophiles **45a**–**l** in hand, we shifted our focus to the exploration of the Diels–Alder cycloadditions (Table 4). As we wanted to exploit a diene that is readily available, we utilized the commercially available 1-methoxy-1,3-cyclohexadiene (**17**) for the cycloaddition process. We were pleased to find that this approach for biaryl synthesis proved highly effective. We observed formation of the tetra-ortho-substituted

(19) (a) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413–2416. (b) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550–9561.
(20) Buchwald, S. L.; Ali, M. H. *J. Org. Chem.* **2001**, *66*, 2560–2565.

Table 3. Synthesis of the Disubstituted, Carbonyl-Containing Alkynes



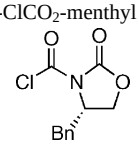
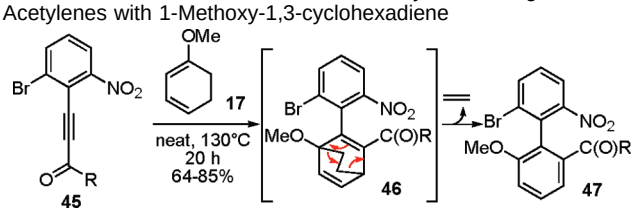
entry	electrophile (Cl-E)	yield (%)
a	$ClCO_2Me$	92
b	$ClCO_2Et$	91
c	$ClCO_2CH_2CCl_3$	68
d	ClC(O)-*t*-Bu	74
e	ClC(O)Ph	67
f	ClC(O)-*p*-Cl-C_6H_4	59 (borsm)
g	ClC(O)-*p*-NO_2-C_6H_4	35
h	$ClC(O)NMe_2$	65
i	$ClC(O)NPh_2$	56
j	ClC(O)-*N*-morpholinyl	89
k	(-)-$ClCO_2$-menthyl	63
l		61

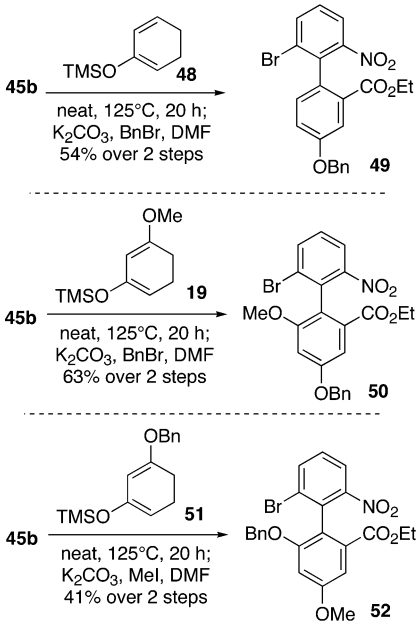
Table 4. Diels–Alder Reactions of Carbonyl-Containing Acetylenes with 1-Methoxy-1,3-cyclohexadiene



entry	R	yield (%)
a	OMe	82
b	OEt	85
c	OCH_2CCl_3	64
d	*t*-Bu	81
e	Ph	71
f	*p*-Cl-C_6H_4	64
g	*p*-NO_2-C_6H_4	complex mixture
h	NMe_2	75
i	NPh_2	72
j	*N*-morpholinyl	83

biaryls **47** in good to excellent yield (64–85%). In the vast majority of cases, a single regioisomer **47** was observed. We attribute this fact to the directing ability the ortho-nitrophenyl substitution—even in the presence of additional strongly electron-withdrawing groups. The regiochemistry of each biaryl product **47** was confirmed via HMBC analysis. Further confirmation was obtained via X-ray crystallographic analysis of compound **47b**. On certain aromatic ketone systems (entry f), a minor amount (<10%) of the alternate regioisomer was observed. We attempted to push the trend further with the more electron-deficient alkyne **45g**; however, a complex mixture of products was observed in its cycloaddition (entry g). This Diels–Alder process is believed to work via initial cycloaddition to the [2.2.2] bicyclic adduct **46** followed by extrusion of ethylene to provide aromatized biaryl **47**. It should also be noted that we could observe the bicyclic intermediate **46** if the reaction is conducted at lower temperatures (50 °C, 16 h). In the case of the ethyl ester **45b**, the ratio between the two diastereomers is 1.5:1 as

Scheme 7. Diene Scope in the Carbonyl-Containing Diels−Alder Reactions

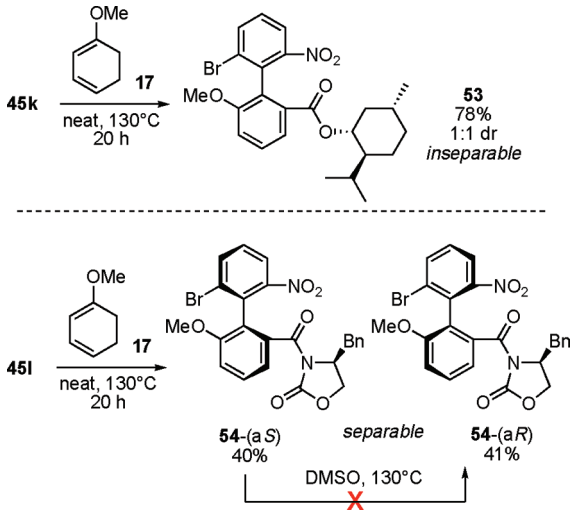


judged by ^{1}H NMR. These diastereomers are the result of diene approach of the acetylene from the same side as the NO_2 group (endo approach) or the opposite side from the NO_2 group (exo approach). Subsequent heating at higher temperatures (130 °C, 16 h) did induce ethylene extrusion to produce the desired biaryl **47** as a single regioisomer.

We also explored the diene scope of this protocol using the dienophile **45b** (Scheme 7). In addition to the mono-oxygenated cyclic diene **48**, we found that 1,3-bis-oxygenation is tolerated in the cycloaddition process (dienes **19** and **51**). The diene **51**[21] was employed to provide benzyloxy substitution at the ortho phenolic position. We initially screened acyclic dienes such as Brassard's diene, but no cycloadduct was observed. It is apparent from our efforts that a cyclic diene moiety is required to achieve effective cycloaddition with these carbonyl-containing dienophiles **45**. We are unsure of an exact rationale for this result; however, one possible explanation is that the acyclic dienes (e.g., Brassard's diene **3**) may undergo a stepwise or [2+2] addition to the acetylene followed by decomposition of the resultant intermediate. Support for this possibility can be seen in the fact that consumption of the dienophile is observed with diene **3**. Additionally, some of the carbonyl-containing dienophiles **45** have proven significantly more sensitive than the phosphorus-containing series; the esters **45a−c** require purification on Florisil and the oxazolidinone **45l** is purified on SiO_2 in the presence of 1% Et_3N in order to avoid decomposition.

Synthesis of Atropisomers. We are beginning to expand the scope of this Diels−Alder process to include the rapid synthesis of enantiomerically pure atropic isomers (Scheme 8). Use of the menthol ester **45k** did generate a 1:1 mixture of diastereomeric atropisomers (78%); however, we were unable to separate the two compounds. Fortunately, when the benzyl oxazolidinone-containing dienophile **45l** was allowed to react with the commercially available diene **17**, we observed chromatographically separable atropic diastereomers **54**-(a*S*) and **54**-(a*R*) (1:1). The absolute configuration of the atropic center of chirality was assigned via the found X-ray crystal structure of **54**-(a*S*) (Figure 3). The atropic integrity is maintained even with prolonged heating at 130 °C (24 h, no change). Other oxazolidinones were screened including the *tert*-butyl-derived oxazolidinone and SuperQuat[22] but led to similar results (1:1 ratio of diastereomers).

Scheme 8. Use of Chiral Dienophiles in the Carbonyl-Containing Diels−Alder Reactions



Synthesis of Biaryl-Derived, Enantioenriched Amino Alcohol and Lactam. With rapid entry into the axially chiral biaryl compounds via the Diels−Alder approach, we wanted to explore the ability to additionally functionalize the scaffold. We were pleased to find that reduction of the oxazolidinone **54**-(a*S*) with $LiBH_4$, MeOH at 0 °C generated the alcohol **55** in good yield (Scheme 9). Use of alternate reduction systems (e.g., $LiAlH_4$) led to complex mixtures. Reduction of both the nitro and the carbonyl moieties may be accomplished in a single step by simply conducting the same reduction at reflux to yield the anilino alcohol **56** in reasonable yield (64%). Amino alcohol **56** represents one of the first reported examples of a potential organocatalyst possessing solely axial chirality—particularly with anilino-derived structures.[23] Recent reports on the organocatalytic ability of anilines have been disclosed.[24] Alternatively, we found that reduction of the nitro moiety **54** with Zn/AcOH induced formation of the highly strained lactam **57** in modest yield. The structure of *ent*-**57** (Figure 4) was determined by single-crystal X-ray diffraction methods. It should be noted from the X-ray structure that the bromide and methoxy moieties are oriented significantly out of the plane—with a dihedral angle between the bromide and the methoxy group of 35.3° (with respect to the plane created by the neighboring atoms, Figure 4). Interestingly, reduction of the nitro moiety with

(21) Diene **46** could be readily prepared from 1,3-cyclohexanedione in two steps [BnOH, PTSA (2.5 mol %), PhMe, Dean−Stark trap, reflux, 20 h, 86%; LDA, THF, −78 °C, then TMSCl, 99%]. See ref 7.

(22) Bull, S. D.; Davies, S. G.; Jones, S.; Sanganee, H. J. *J. Chem. Soc., Perkin Trans.* **1999**, *1*, 387−398.

(23) Despite the wealth of research that has been directed toward organocatalysis, relatively little attention has been focused on the use of axial chirality for asymmetric organocatalytic induction. (a) For a recent series of reviews in the area, see: *Acc. Chem. Res.* **2004**, *37(8)*, 487−631. (b) It is important to acknowledge the pioneering work by Maruoka in the area of axial chiral organocatalysts. Kano, T.; Tokuda, O.; Takai, J.; Maruoka, K. *Chem. Asian J.* **2006**, *1*, 210−215.

(24) (a) Dirksen, A.; Hackeng, T. M.; Dawson, P. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 7581−7584. (b) Dirksen, A.; Dirksen, S.; Hackeng, T. M.; Dawson J., P. E. *J. Am. Chem. Soc.* **2006**, *128*, 15602−15603. (c) See also: Borman, S. *Chem. Eng. News* **2006**, *84* (49), 11.

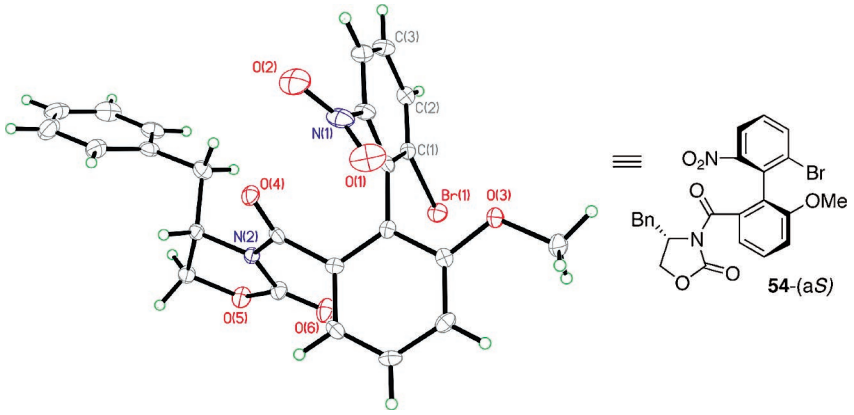


Figure 3. ORTEP representation of the X-ray structure of biaryl **54**-(a*S*).

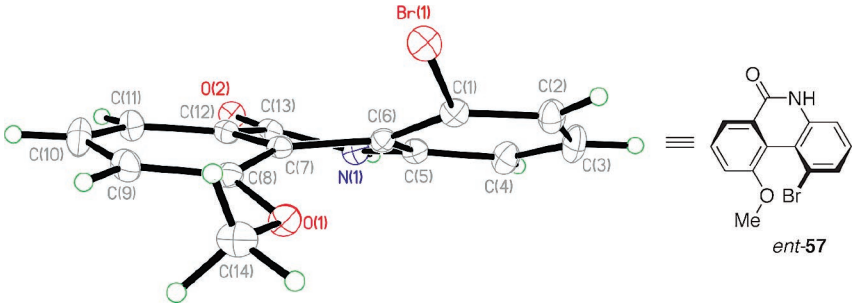
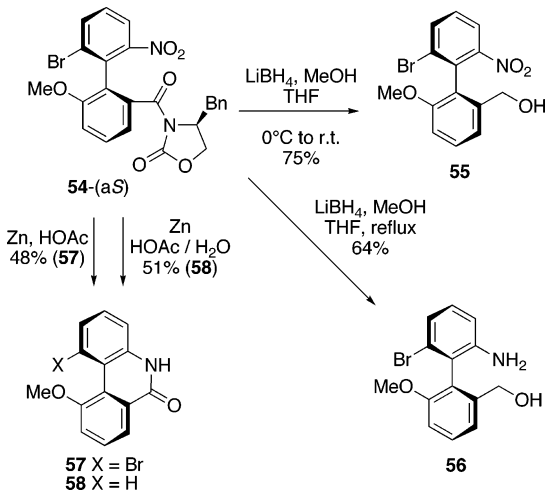


Figure 4. ORTEP representation of the X-ray structure of lactam *ent*-**57**.

Scheme 9. Synthesis of Potential Organocatalysts



Zn in *aqueous* HOAc produced the dehalogenated lactam derivative **58**.

Conclusion

This article demonstrates the utility of the DAB methodology to provide highly functionalized, useful biaryls in an expedient fashion (typically three to four steps). We have successfully synthesized entire classes of biaryl compounds that would not be readily accessible from alternative methods. In fact, the successful construction of biaryl compounds possessing four different atoms (N, Cl/Br, O, and P for the phosphorus series and N, Br, O, and C for the carbonyl series) at the four ortho positions has not been accomplished by any other method. One intriguing feature of these Diels−Alder processes is their ability to construct sterically challenging functionality under quite mild conditions. In many cases, the cycloaddition sequence appears to work better on the more substituted systems. Additionally, the strong directing ability of the ortho nitro moiety, even in the presence of ketones, esters, and amides is noteworthy.

We have demonstrated the utility of this methodology for the synthesis of a novel ligand system for C−C and C−N couplings. The first-generation ligand **34** has demonstrated early potential for facilitating challenging cross-couplings. This example embodies the power of the DAB methodology—the ability to construct sterically demanding biaryl structures not accessible from traditional metal-mediated methods. This methodology provides an ideal complement to the powerful coupling technologies developed by Fu, Buchwald, Hartwig, and others[1,2] for the synthesis of complex biaryl structures. The combination of these two technologies has the potential to lead to the development of new ligand systems that may facilitate cross-coupling processes not currently accessible from the existing ligand systems.

The carbonyl-containing biaryl series has been exploited for the synthesis of a series of ester-, ketone-, and amide-containing, tetra-ortho-substituted biaryls. The strong directing ability of the ortho nitro moiety is able to guide the cycloaddition in the presence of an array of carbonyl derivatives. The first reported case of enantioenriched biaryls from our DAB protocol is demonstrated using a benzyl oxazolidinone. Subsequent conversion to a series of derivatives, including the axially chiral, biaryl anilino alcohol **56**, showcases the flexibility of this methodology. Future applications of this technology will be reported in due course.

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Supporting Information Available: All experimental procedures; ^{1}H and ^{13}C spectra of all new compounds; crystallographic data with details of data collections and refinements for crystal structures of the compounds **5b**, **14a**, **14c**, **28a**, **28e**, **28f**, **34**·HCl, **47b**, **54-(a*S*)**, *ent*-**57** and the corresponding CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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