Organic LETTERS

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Regioselective 1,4-Conjugate Addition of Grignard Reagents to Nitrodienes in the Presence of Catalytic Amounts of Zn(II) Salts

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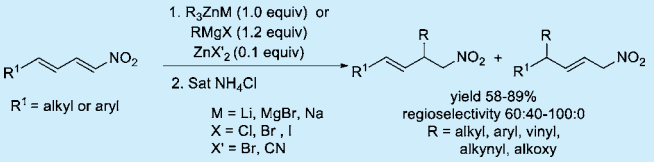
Supporting Information

ABSTRACT: Grignard reagents undergo facile regioselective 1,4-conjugate addition to nitrodienes in the presence of catalytic amounts of Zn(II) salts with excellent yields. A wide range of ligands such as alkyl, aryl, heteroaryl, allyl, vinyl, 1-alkynyl, and alkoxy ligands were transferred, while a thiolate ligand afforded 1,6-regioselectivity. The reactions were successfully carried out on δ-alkyl- or aryl-substituted α,β,γ,δ-diunsaturated nitrodiene substrates. Regioselectivity is minimally influenced by temperature or choice of solvent.



The control of regio-, stereo-, and chemoselectivity in the reactions of small, highly functionalized molecules provides rich opportunities for generating highly substituted and functionalized molecular synthons.[1,2] The conjugate addition of carbon nucleophiles to Michael acceptors is a ubiquitous reaction for construction of carbon−carbon bonds in organic chemistry,[3] and Michael acceptors containing conjugated dienes[4−6] pose problems of regioselective control. Numerous developments have been reported for the conjugate addition reactions of nitroalkene−Michael acceptors for the synthesis of nitrogen-containing molecules, which are often richly endowed with biological activity.[7] The most widely studied nitro alkene-Michael acceptors include simple nitroalkenes,[8] α,β,γ,δ-nitrodienes,[8d,9−11] and nitroenynes[8d,12] where the conjugated nitrodienes and nitroenynes give a mixture of products in the absence of catalysts arising from competitive nonregioselective 1,4- and 1,6-addition pathways.[9−11]

Although a large number of organocatalytic procedures for the regio- and stereoselective conjugate addition of nucleophiles to nitrodienes have been developed, they have largely involved soft nucleophiles such as enolates, enamines, and silyl enol ethers. Chiral proline,[9a−d] bifunctional amine−thiourea derivatives,[9e−i] cinchona alkaloids,[9j,k] and amino acid[9l,m] catalysts have been employed for enantioselective 1,4-conjugate addition reactions of carbonyl substrates to nitrodienes with high efficiency. The utilization of nitrodienes in transition-metal-catalyzed enantioselective 1,4-conjugate addition reactions of malonate enolates,[9n] Friedel−Crafts alkylation of indole,[9o] diastereoselective Morita−Baylis−Hillman reactions[10] of carbonyl compounds, and the Rauhut−Currier reaction[11] of methyl vinyl ketone (MVK) have also been reported recently.

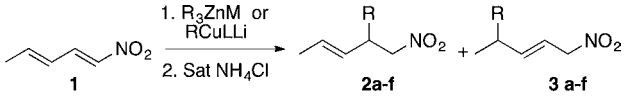
The use of organometallic reagents for regio- and stereoselective 1,4-conjugate additions to nitrodienes is rather limited. A singular report on 1,4-additions of triorganoaluminum reagents[13] to nitroalkenes was followed recently by a report for the regio- and enantioselective 1,4- or 1,6-conjugate addition reactions of trialkylaluminum reagents to nitrodienes employing catalytic amounts of Cu(I) salts and ferrocene based chiral ligands.[8d,12c] We now report our results on the regioselective 1,4-conjugate addition of Grignard reagents to nitrodienes in the presence of catalytic amounts of zinc(II) salts.

We first examined the 1,4-conjugate addition reactions of stoichiometric organozincate reagents to (*E*)-1-nitro-2,4-pentadiene (**1**). Although 1,4-conjugate addition was the favored pathway, a mixture of 1,4- and 1,6-addition products was observed (Table 1, entries 1−5 and 8−14) when trialkylzincate reagents were employed. Treatment of nitrodiene **1** with $^{n}Bu_3ZnLi$ gave slightly better regioselectivity at lower temperatures (entry 1 vs 2) and in less polar solvents (entries 3 and 4), but slightly decreased regioselectivity was observed when the counterion was changed from Li^+ to $MgBr^+$ (entries 5 and 9). As expected, the dialkyl or alkyl(cyano)-cuprate reagents gave exclusively the 1,6-addition product (entries 6 and 7).[6] Although slightly higher regioselectivity was obtained with the less reactive Me_3ZnLi (entry 8), little to no regioselectivity was observed for $^{t}Bu_3ZnLi$ in either polar (entries10 and 11) or nonpolar (entry 12) solvents. Good regioselectivity could be achieved by utilization of the mixed triorganozinate $^{t}BuZnMe_2Li$ (entries 13 and 14), which was also observed for $^{i}PrZnMe_2MgBr$ (entry 9). Surprisingly, the reaction of sodium tributoxy zincate with nitrodiene **1** also gave exclusively the 1,4-adduct in good yield and without a trace of the 1,6-addition product being formed (entry 15), while the utilization of $(^{n}PrS)_3ZnNa$ under identical reaction conditions gave the 1,6-adduct with minor amounts of the 1,4-addition product (entries 16 and 17).[14]

Encouraged by these preliminary results involving the reaction of stoichiometric organozincate reagents with nitrodiene **1**, we sought to reduce the amounts of organometallic reagents used [RLi or Grignard reagent (3.0 equiv), $ZnBr_2$ (1.0 equiv)] by developing a procedure catalytic in the Zn(II) salt

Received: January 13, 2014
Published: February 19, 2014

Table 1. Regioselective Conjugate Addition of Organozincate/Organocuprate Reagents to Nitrodiene 1



R = alkyl
M = Li, MgBr or Na

a R = ^{n}Bu **d** R = ^{t}Bu
b R = Me **e** R = ^{n}BuO
c R = ^{i}Pr **f** R = ^{n}PrS

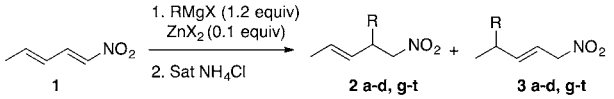
entry	R_3ZnM or RCuLLi[a]	solvent[b]	temp °C (h)[c]	% yield (2 + 3)[d]	regio (2:3)[e]
1	$^{n}Bu_3ZnLi$	A	−40 (12)	78	82:18
2	$^{n}Bu_3ZnLi$	A	−78 (3)[f]	81	84:16
3	$^{n}Bu_3ZnLi$	B	−78 (3)[f]	78	87:13
4	$^{n}Bu_3ZnLi$	C	−78 (3)[f]	72	88:12
5	$^{n}Bu_3ZnMgBr$	A	−78 (12)	74	78:22
6	$^{n}Bu_2CuLi$	A	−78 (12)	77	0:100
7	$^{n}BuCuCNLi$	A	−78 (12)	55	0:100
8	Me_3ZnLi	A	−78 (12)	71	90:10
9	$^{i}PrZnMe_2MgBr$	A	−78 (12)	78	88:12
10	$^{t}Bu_3ZnLi$	A	−40 (3)	80	50:50
11	$^{t}Bu_3ZnLi$	A	−78 (3)	72	56:44
12	$^{t}Bu_3ZnLi$	C	−78 (3)[f]	71	55:45
13	$^{t}BuZnMe_2Li$	A	−78 (6)	73	78:22
14	$^{t}BuZnMe_2Li$	A	−78 (3)[f]	69	92:8
15	$(^{n}BuO)_3ZnNa$	A	−20 (12)	81	100:0
16	$(^{n}PrS)_3ZnNa$	A	25 (1)	78	6:94
17	$(^{n}PrS)_3ZnNa$	A	−78 (6)	79	5:95

[a]1−1.5 equiv of reagents was used. [b]Solvent: A = THF, B = CH_2Cl_2, C = toluene. [c]Reaction was run at the indicated temperature and allowed to warm to room temperature over the indicated time unless otherwise noted. [d]Combined yield of both regioisomers. [e]Regioisomeric ratio was determined from integration of the ^{1}H NMR absorptions of vinyl hydrogens or peak height of the vinyl carbon absorptions in the ^{13}C NMR spectrum. [f]Reaction was run and quenched at the indicated temperature.

(Table 2). In a control experiment, reaction of ^{n}BuMgCl (1.0 equiv) with nitrodiene **1** in the absence of Zn(II) salts gave moderate yields of conjugate adducts with poor regioselectivity (Table 2, entry 1). When ^{n}BuMgCl (1.2 equiv) was reacted with nitrodiene **1** in the presence of catalytic amounts of zinc bromide (0.1 equiv), good yields and regioselectivity for the 1,4-conjugate adduct was observed (entries 2−5) with the degree of regioselectivity being largely independent of solvent polarity but slightly higher when conducted at lower temperatures. Similar results were obtained for the methyl, isopropyl, and benzyl Grignard reagents (entries 6−8), although the benzyl Grignard reagent gave significantly lower regioselectivity at higher temperatures (entries 9 and 10) in Et_2O with the poor or noncoordinating solvents Et_2O and PhMe giving slightly lower regioselectivities (entries 11 and 12) than the more coordinating THF (entry 8) at −78 °C. Allyl Grignard reagents gave good yields and good regioselectivity in both coordinating (e.g., THF or Et_2O) and noncoordinating (e.g., CH_2Cl_2) solvents (entries 13−15).

These encouraging results involving regioselective 1,4-conjugate addition reactions of alkyl Grignard reagents with nitrodiene **1** mediated by $ZnBr_2$ catalysis prompted us to examine the reaction of aryl Grignard reagents with nitrodiene **1** in the presence of catalytic amounts of zinc(II) salts. Contrary to prior observations,[2a] the reaction of PhMgBr with nitrodiene **1** in Et_2O or CH_2Cl_2 gave excellent yields of the

Table 2. 1,4-Conjugate Addition of Grignard Reagents to 1 Catalyzed by Zn(II) Salts



a R = ^{n}Bu- **i** R = Ph- **o** R = 2-furyl-
b R = Me- **j** R = 2-MeC_6H_4- **p** R = 2-thienyl-
c R = ^{i}Pr- **k** R = 1-naphthyl- **q** R = 2-(1-Me)pyrrolyl-
d R = ^{t}Bu- **l** R = 4-$MeOC_6H_4$- **r** R = ^{n}BuCH=CH-
g R = Bn- **m** R = 4-$Me_2NC_6H_4$- **s** R = ^{n}BuC≡C-
h R = CH_2=$CHCH_2$- **n** R = 5-(1-Me)indolyl- **t** R = PhC≡C-

entry	R[a]	solvent[b]	temp °C (h)[c]	% yield (2 + 3)[d]	regio (2:3)[e]
1	^{n}Bu-[f]	A	−78 (3)	65	65:35
2	^{n}Bu-	A	−40 (12)	81	88:12
3	^{n}Bu-	A	−78 (2)	83	90:10
4	^{n}Bu-	B	−78 (2)	87	91:9
5	^{n}Bu-	C	−78 (2)	86	92:8
6	Me-	A	−78 (3)	75	91:9
7	^{i}Pr-	A	−78 (3)	76	90:10
8	Bn-	A	−78 (3)	77	95:5
9	Bn-	D	0 (12)	85	67:33
10	Bn-	D	−20 (12)	86	76:24
11	Bn-	D	−78 (3)	89	82:18
12	Bn-	C	−78 (3)	72	78:22
13	CH_2=$CHCH_2$-	A	−78 (2)	74	95:5
14	CH_2=$CHCH_2$-	D	−78 (3)	85	96:4
15	CH_2=$CHCH_2$-	B	−78 (3)	89	96:4
16	Ph-	D	−78 (12)	83	80:20
17	Ph-	B	−40 (3)	77	93:7
18	Ph-[g]	B	−40 (3)	85	98:2
19	1-naphthyl-	D	−20 (12)	83	100:0
20	2-MeC_6H_4-	B	−78 (3)	87	92:8
21	*p*-$MeOC_6H_4$-[g]	B	−20 (12)	73	100:0
22	*p*-$Me_2NC_6H_4$-	E	−78 (12)	72	100:0
23	5-(1-Me)indolyl-	D	−20 (12)	73	100:0
24	2-furyl-	D	0 (12)	70	100:0
25	2-furyl-	D	−40 (12)	83	100:0
26	2-thienyl-	D	0 (12)	75	100:0
27	2-thienyl-	D	−20 (12)	81	100:0
28	2-(1-Me)pyrrolyl-	F	−20 (12)	79	100:0
29	^{n}BuCH=CH-	D	−78 (3)	83	100:0
30	^{n}BuC≡C-	D	−20 (12)	76	100:0
31	PhC≡C-	D	−20 (12)	87	72:28
32	PhC≡C-[g]	D	−20 (12)	83	93:7

[a]$ZnBr_2$ (0.1 equiv) was used unless otherwise noted. [b]Solvent: A = THF. B = CH_2Cl_2. C = toluene. D = Et_2O. E = THF:CH_2Cl_2 (1:1). *F* = THF:Et_2O (1:3). [c]Reagents were added at the indicated temperature and warmed to 25 °C over the indicated time. [d]Combined yield of both regioisomers. [e]Regioisomeric ratios were determined from integration of ^{1}H NMR absorptions of vinyl hydrogens or peak height of the vinyl carbon absorptions in ^{13}C NMR spectrum. [f]Reaction run in the absence of Zn(II) salts. [g]$Zn(CN)_2$ (0.1 equiv) was used.

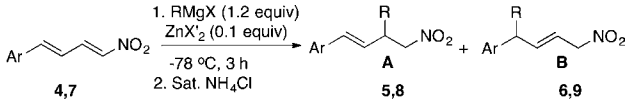
conjugate adduct with modest regioselectivity in Et_2O (entry 16) and excellent regioselectivity at −40 °C in CH_2Cl_2 (entries 17 and 18). Significant production of biphenyl was not observed in these reactions, and $Zn(CN)_2$ offered no advantages over $ZnBr_2$ (entries 17 and 18). The protocol could be readily extended to polyaromatic (entry 19), electron-rich aryl (entries 20−23), and heteroaryl (entries 24−28) Grignard reagents affording exclusively the 1,4-adducts. In these

dx.doi.org/10.1021/ol500114m | *Org. Lett.* 2014, 16, 1362−1365

reactions, the regioselectivity did not appear sensitive to temperature (entries 17−19, 21, 23−28, and 30−32). Surprisingly, an alkynyl Grignard reagent was also successfully transferred to nitrodiene **1** when the catalytic procedure was employed since in prior work[2a] the alkynyl ligand acted as a nontransferable ligand. Although, ^{n}BuC≡CMgBr gave exclusively the 1,4-adduct in Et_2O (entry 30), the more electron deficient PhC≡CMgBr gave good yields but poor regioselectivity (entry 31) under identical reaction conditions. Utilization of $Zn(CN)_2$ (0.1 equiv) in the reaction of PhC≡CMgBr with nitrodiene **1**, however, gave excellent yields and regioselectivity for the major 1,4-adduct (entry 32).

In an attempt to extend substrate scope of the reactions, (*E*)-1-nitro-4-phenyl-1,3-butandiene (**4**) and (*E*)-1-nitro-4-(4-methoxyphenyl)-1,3-butandiene (**7**) were synthesized and reacted with Grignard reagents using a procedure with catalytic zinc(II) salts. The reaction of ^{n}BuMgCl (1.2 equiv) with **4** in the presence of catalytic amounts of zinc cyanide (0.1 equiv) in both coordinating (i.e., THF) and noncoordinating solvents (i.e., CH_2Cl_2, toluene) was investigated. In all of these solvents, moderate yields but poor regioselectivity of the 1,4-adduct were observed (Table 3, entries 1−3, 63−67%, 1,4 vs 1,6; 78:22−80:20). Application of identical reaction conditions for the reaction of PhMgCl (1.2 equiv) with **4** in THF gave moderate yields but poor regioselectivity (entry 4, 66%, 1,4:1,6; 60:40). Utilization of zinc cyanide as a source of Zn(II) ion or use of a noncoordinating solvent (i.e., toluene) did not change the yields or regioselectivity of the conjugate addition product (entries 5 and 6). The reaction of ^{n}BuMgCl with **7** gave good yields of conjugate addition products with poor regioselectivity (entry 7, 73%, 1,4:1,6; 78:22), while PhMgCl gave exclusive 1,4-conjugate adduct in good yield (entry 8, 71%, 1,4:1,6; 100:0). Vinyl Grignard reagents also gave good yields and exclusively the 1,4-conjugate addition product (entry 9, 73%, 1,4:1,6; 100:0) under identical reaction conditions.

Table 3. 1,4-Conjugate Addition of Grignard Reagents to Aryl Nitrodienes Catalyzed by Zn(II) Salts



4,5,6 Ar = C_6H_5-
7,8,9 Ar = 4-MeOC_6H_4-

a R = ^{n}Bu-
b R = Ph-
c R = ^{n}BuCH=CH-

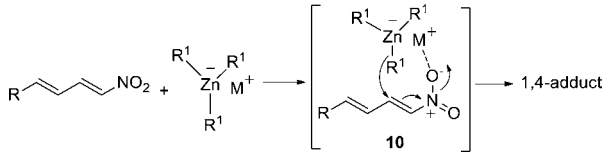
entry	diene	R-[a]	solvent[b]	% yield[c] (A + B)	regio[d] (A:B)
1	**4**	^{n}Bu-	A	65	78:22
2	**4**	^{n}Bu-	B	67	80:20
3	**4**	^{n}Bu-	C	63	78:22
4	**4**	Ph-[e]	A	66	60:40
5	**4**	Ph-	A	77	65:35
6	**4**	Ph-	C	58	60:40
7	**7**	^{n}Bu-	A	73	78:22
8	**7**	Ph-[e]	A	71	100:0
9	**7**	^{n}BuCH=CH-[e,f]	A	73	100:0

[a] $Zn(CN)_2$ (0.1 equiv) was used as catalyst unless otherwise noted. [b] Solvent: A = THF. B = CH_2Cl_2. C = toluene. [c] Combined yield of both regioisomer. [d] Regioisomeric ratios were determined from integration of the ^{1}H NMR absorptions of the vinyl hydrogen or the peak height of the vinyl carbon absorptions in the ^{13}C NMR spectrum. [e] $ZnBr_2$ (0.1 equiv) was used. [f] Grignard reagent was prepared by halogen−metal exchange of the corresponding vinyl iodide with ^{n}BuLi (1.0 equiv) followed by treatment with $MgBr_2$.

Although complex **10** has been invoked[15] to account for the tendency of organozinc reagents to undergo 1,4-addition to α,β-unsaturated carbonyl compounds in contrast to the 1,2-addition reactivity pathway of Grignard and organolithium reagents and could explain the preference for 1,4-selectivity, the model does not fully comport with our experimental data. Contrary to expectations, the 1,4:1,6-regioselectivity is relatively insensitive to solvent-coordinating ability [e.g., THF vs CH_2Cl_2 or PhMe (DN = 20−0):[16] Table 1, entries 2 vs 3−4, 11 vs 12; Table 2, entries 3 vs 4−5, 8 vs 11−12, and 13 vs 14−15; Table 3, entries 2 vs 3−4, 5 vs 6] where a contact ion-pair (CIP) for the zincate reagent[17] in CH_2Cl_2 or PhMe should favor greater 1,4:1,6-selectivity and a solvent separated ion-pair (SSIP) in THF[16] should induce lower selectivity.[2a,17]

Calculations indicate that the d-orbitals on organo-Zn(II) species are low lying in comparison[15,18] to those of organocuprates (e.g., R_2CuM) so that the organo ligands act as the nucleophiles in the former while the Cu atom acts as the nucleophile in the latter. Thus, the zinc reagents follow a pathway of carbozincation[18] while the cuprate reagents undergo oxidative addition and favor 1,6-addition via $\sigma-\pi$-allyl-σ-Cu(III) rearrangements. The preference for zincate 1,4-addition could be rationalized by differential charge density or orbital coefficient magnitudes at the γ- and δ-positions (Scheme 1). The latter correctly rationalizes regiochemistry in

Scheme 1. Mechanistic Rationale for 1,4-Addition



frontier molecular orbital (FMO) models.[19] Simple semi-empirical calculations[20] support this view and correctly predict lower 1,4:1,6-regioselectivity for the aryl-substituted nitrodienes **4** and **7**. Charge density considerations also appear consistent with the 1,6-preference of $(^{n}PrS)_3ZnNa$ and 1,4-preference of $(^{n}BuO)_3ZnNa$ (Table 2, entries 16 and 17) in line with HSAB considerations.[15]

In summary, we have successfully developed the first method for the 1,4-conjugate addition of Grignard reagents to $\alpha,\beta,\gamma,\delta$-unsaturated nitrodienes in the presence of catalytic amounts of Zn(II) salts and in the absence of Cu(I) salts. The method is highly 1,4-regioselective for δ-alkyl-substituted nitrodiene **1** showing excellent 1,4-selectivity for alkyl (90:10 to 92:8), benzyl (82:18 to 95:5), allyl (95:5 to 96:4), and alkynyl (93:7 to 100:0) Grignard reagents while displaying exclusive to nearly exclusive 1,4-selectivity for aryl (98:2 to 100:0), heteroaryl (100:0), and vinyl (100:0) Grignard reagents. Although there are no uniform patterns, choice of solvent, Zn(II) salt, and reaction temperature can be manipulated to increase 1,4-regioselectivity in those cases where initial experimenation led to 1,4:1,6 ratios below 90:10. δ-Substituted aryl nitrodienes **4** and **7** generally display reduced 1,4-selectivity, although a 4-methoxyphenyl substituent (i.e., **7**) did afford exclusive 1,4-selectivity with phenyl and alkenyl Grignard reagents. The scope of the method was also expanded to heteroatom ligands wherein alkoxyzincate reagents gave exclusive 1,4-addition and alkylthiolatozincates gave high 1,6-selectivity (95:5). The

dx.doi.org/10.1021/ol500114m | Org. Lett. 2014, 16, 1362−1365

conjugate addition of alkynyl and heteroatom ligands are particularly challenging for Cu(I) salts. Control experiments confirmed that the reactions were indeed catalyzed by zinc(II) salts.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedures, data reduction, ^{1}H and ^{13}C NMR spectra for **1**, **2a−t**, **3a,g,i,t**, **4**, **5a,b**, **7**, and **8a−c** are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Support of the NSF Chemical Instrumentation Program for purchase of a JEOL 500 MHz NMR instrument is gratefully acknowledged (CHE-9700278).

■ REFERENCES

(1) For a review on divergent synthetic strategy, see: Serba, C.; Winssinger, N. *Eur. J. Org. Chem.* **2013**, 4195−4214.

(2) (a) Dhakal, R. C.; Dieter, R. K. *J. Org. Chem.* **2013**, *78*, 12426−12439. (b) Guo, F.; Dhakal, R. C.; Dieter, R. K. *J. Org. Chem.* **2013**, *78*, 8451−8464. (c) Dieter, R. K.; Huang, Y.; Guo, F. *J. Org. Chem.* **2012**, *77*, 4949−4967. (d) Dieter, R. K.; Guo, F. *J. Org. Chem.* **2009**, *74*, 3843−3848. (e) Dieter, R. K.; Guo, F. *Org. Lett.* **2008**, *10*, 2087−2090.

(3) (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Reactions*; Pergamon: Oxford, 1992. (b) Ballini Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933−971.

(4) For reviews on conjugate addition to electron-deficient dienes, see: (a) Silva, E. M. P.; Silva, A. M. S. *Synthesis* **2012**, *44*, 3109−3128. (b) Csaky, A. G.; de le Herran, G.; Murcia, M. C. *Chem. Soc. Rev.* **2010**, *39*, 4080−4102.

(5) For a review on conjugated nitrodienes, see: Ballini, R.; Araujo, N.; Gil, M. V.; Roman, E.; Serrano, J. A. *Chem. Rev.* **2013**, *113*, 3493−3515.

(6) For a review on copper-mediated 1,6-conjugate additions, see: Krause, N.; Aksin-Artok, O. In *Chemistry of Organocopper Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: New York, 2009; Part 2, pp 857−879. For mechanistic studies, see: (a) Ueerdingen, M.; Krause, N. *Tetrahedron* **2000**, *56*, 2799−2804. (b) Yoshikai, N.; Yamashita, T.; Nakamura, E. *Asian—J. Chem.* **2006**, *1*, 322−330.

(7) (a) Bäckvall, J.; Karlsson, U.; Chinchilla, R. *Tetrahedron Lett.* **1991**, *32*, 5607−5610 and references cited therein. (b) Ballini, R.; Bosica, G.; Gil, M. V.; Román, E.; Serrano, J. A. *Tetrahedron: Asymmetry* **2002**, *13*, 1773−1787.

(8) (a) Schäfer, H.; Seebach, D. *Tetrahedron* **1995**, *51*, 2305−2324. (b) Alexakis, A.; Benhaim, C. *Org. Lett.* **2000**, *2*, 2579−2581. (c) Rimkus, A.; Sewald, N. *Synthesis* **2004**, *2004*, 135−146. (d) Tissot, M.; Alexakis, A. *Chem.—Eur. J.* **2013**, *19*, 11352−11363.

(9) (a) List, B.; Pojarliev, P.; Martin, H. *Org. Lett.* **2001**, *3*, 2423−2425. (b) Hayashi, Y.; Okana, T.; Aratake, S.; Hazelard, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 4922−4925. (c) Belot, S.; Massaro, A.; Tenti, A.; Mordini, A.; Alexakis, A. *Org. Lett.* **2008**, *10*, 4557−4560. (d) Belot, S.; Quintard, A.; Krause, N.; Alexakis, A. *Adv. Synth. Catal.* **2010**, *352*, 667−695. (e) He, T.; Qian, J.; Song, H.; Wu, X. *Synlett* **2009**, *2009*, 3195−3197. (f) Ma, H.; Liu, K.; Zhang, F.; Zhu, C.; Nei, J.; Ma, J. *J. Org. Chem.* **2010**, *75*, 1402−1409. (g) Chen, J.; Fu, L.; Zou, Y.; Chang, N.; Rong, J.; Xiao, W. *Org. Biomol. Chem.* **2011**, *9*, 5280−5287. (h) Tsakos, M.; Kokotos, C. G. *Eur. J. Org. Lett.* **2012**, *2012*, 576−580. (i) Tan, B.; Lu, Y.; Zeng, X.; Chua, P. J.; Zhong, G. *Org. Lett.* **2010**, *12*, 2682−2685. (j) Tan, B.; Chua, P. J.; Li, Y.; Zhong, G. *Org. Lett.* **2008**, *10*, 2437−2440. (k) Tripathi, C. B.; Kayal, S.; Mukherjee, S. *Org. Lett.* **2012**, *14*, 3296−3299. (l) Nugent, T. C.; Shoaib, M.; Shoaib, A. *Org. Biomol. Chem.* **2011**, *9*, 52−56. (m) Biswas, A.; De Sarkar, S.; Tebben, L.; Studer, A. *Chem. Commun.* **2012**, *48*, 5190−5192. (n) Evans, D. A.; Mito, S.; Seidel, D. *J. Am. Chem. Soc.* **2007**, *129*, 11583−11592. (o) Peng, J.; Du, D. *Eur. J. Org. Chem.* **2012**, *2012*, 4042−4151.

(10) Deb, I.; Shanbhag, P.; Mobin, S. M.; Namboothiri, I. N. N. *Eur. J. Org. Chem.* **2009**, *2009*, 4091−4101.

(11) Shanbhag, P.; Nareddy, P. R.; Dadwal, M.; Mobin, S. M.; Namboothiri, I. N. N. *Org. Biomol. Chem.* **2010**, *8*, 4867−4873.

(12) (a) Trost, B. M.; Hisaindee, S. *Org. Lett.* **2006**, *8*, 6003−6005. (b) Belot, S.; Vogt, K.; Besnard, C.; Krause, N.; Alexakis, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 8923−8926. (c) Tissot, M.; Mulller, D.; Belot, S.; Alexakis, A. *Org. Lett.* **2010**, *12*, 2770−2773. (d) Uraguchi, D.; Kinoshita, N.; Kizu, T.; Ooi, T. *Synlett* **2011**, *2011*, 1265−1267.

(13) Menicagli, R.; Guagnano, V.; Malanga, C. *Gazz. Chim. Ital.* **1992**, *122*, 487−488.

(14) For organocatalytic 1,4-addition of aliphatic thiols to nitrodiene, see: Kowalczyk, R.; Nowak, A. E.; Skarzewski, J. *Tetrahedron: Asymmetry* **2013**, *24*, 505−514.

(15) Uchiyama, M.; Nakamura, S.; Furuyama, T.; Nakamura, E.; Morokuma, K. *J. Am. Chem. Soc.* **2007**, *129*, 13360−13361.

(16) For donor numbers (DN), see: Gutmann, V. *Coord. Chem. Rev.* **1976**, *18*, 225−255.

(17) (a) Hevia, E.; Chua, J. Z.; Garcia-Alvarez, P.; Kennedy, A. R.; McCall, M. D. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 5294−5299. (b) Armstrong, D. R.; Clegg, W.; Garcia-Alvarez, P.; McCall, M. D.; Nuttall, L.; Kennedy, A. R.; Russo, L.; Hevia, E. *Chem.—Eur. J.* **2011**, *17*, 4470−4479.

(18) Mori, S.; Hirai, A.; Nakamura, M.; Nakamura, E. *Tetrahedron* **2000**, *56*, 2805−2809.

(19) Fleming, I. *Molecular Orbitals and Organic Chemical Reactions*, reference ed.; John Wiley & Sons: Chichester, UK, 2010; Chapter 4, pp 183−199.

(20) MacSpartan PM3 (WAVEFUNCTION, Inc.: Irvine, CA) calculations give charge differences between C2 and C4 [compound Δ(C2−C4): **1** (+ 0.126), **4** (+ 0.079), and **7** (+ 0.071)] and orbital coefficient differences [compound Δ(C2-C4): **1** (+ 0.7419), **4** (+ 0.00254) and **7** (+ 0.00201)] that qualitatively mirror the observed 1,4:1,6-regioselectivity trends with aryl-substituted nitrodienes giving lower regioselectivity. Hartree−Fock (6-31G**) calculations for **1** gave small negative charge values for C2 and C4 where C4 was less negative than C2 by 0.029 charge units, and the orbital coefficient difference Δ(C2−C4) was +0.03468 so that semiempirical PM3 and ab initio Hartree−Fock calculations gave the same qualitative picture. Caution should be exercised when applying simple MO calculations to rationalize chemical reactivity by "electrostatic terms and electron density alone". See: Schwarz, W. H. E.; Schmidbaur, H. *Chem.—Eur. J.* **2012**, *18*, 4470−4479.