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Copper-Free Asymmetric Allylic Alkylation Using Grignard Reagents on Bifunctional Allylic Bromides

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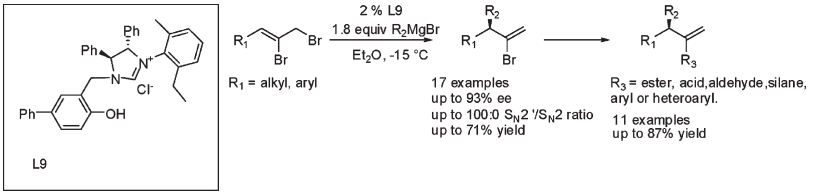
ABSTRACT



A series of substrates containing a vinylic bromide were employed in a copper-free methodology using bidendate NHC ligands. The desired compounds are generally obtained with good enantioselectivity and good regioselectivity. Importantly the copper-catalyzed system afforded a lower enantioselectivity value. The catalytic products could be transformed into a broad scope of new 1,1-disubstituted olefins in a single step transformation without erosion of the enantioselectivity.

In the context of asymmetric allylic alkylation (AAA),[1] the copper-catalyzed AAA turned out to be one of the most attractive and efficient reactions in the enantioselective construction of C−C bonds. Several ligand families, such as phosphoramidites, ferrocene-based ligands, peptide-type ligands, or N-heterocyclic carbenes (NHC), were used to coordinate copper. In addition to a broad substrate scope, a large variety of organometallic reagents such as organoaluminum, organozinc, and Grignard reagents could be used. Among them, the Grignard reagents are easily available nucleophiles and have been applied to a wide range of prochiral substrates.[2] More recently, they have been extended to racemic chiral substrates in DYKAT processes, providing highly enantioenriched products.[3] In most cases, the substrates do not bear other functionalities, and the only handle for molecular complexity lies on the further transformations of the resulting double bond. Examples of functionalized substrates are scarce, with mainly another functional group[4] or an additional unsaturation.[5] A method that could be able to produce enantiomerically enriched S_N2' products, which could be potent

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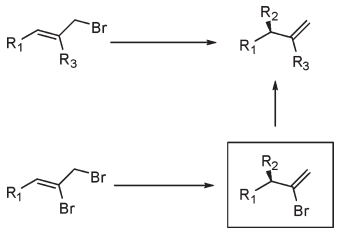
pivotal intermediates toward several new adducts result ing from an AAA reaction, would be very desirable. This achievement could save several steps in the synthesis of substrates and methodology development. We thought that using a halogen binding to a sp^2 carbon may be the candidate of choice for such desired pivotal intermediates (Scheme 1).

Scheme 1. Concept of Versatile Intermediate



In our laboratory, we have extensively used Grignard reagents in combination with copper and phosphoramidite ligands, and very recently, the use of NHC's ligands in a copper-free methodology has proven to be very efficient in the AAA.[6] Having both isomers of the model substrate in hand, we tested the outcome of the reaction on the *Z*-isomer using our NHC's bidendate ligand (Figure 1). Different conditions were screened using copper salt and ligand **L1**, affording poor regioselectivity and reactivity (Table 1, entries 1−2). This disappointing result was not a surprise, as *Z*-isomers are known to react sluggishly in the AAA reaction. By submitting the *E*-isomer using the same ligand **L1** in the copper-free methodology, we obtained an encouraging regioselectivity and enantioselectivity (79/21 in favor of the S_N2' adduct, 65% ee) with a high conversion (Table 1, entry 3). Performing the reaction with copper/NHC ligand **L1** (Table 1, entry 13) or with copper in combination with our best phosphoramidite **L10** (Table 1, entry 14) did not lead to any valuable improvement of the enantioselectivity, while higher regioselectivities were accessed.

The next logical step was the screening of our NHC's library of ligands in a copper-free way in order to try to improve the existing results. The switch from (methyl/methyl) **L1** to more sterically hindered (ethyl/ethyl moiety) **L2** led to a decrease of regioselectivity, enantioselectivity, and reactivity (Table 1, entries 3−4). We then decided to introduce dissymmetry on the blocking part, and this choice turned out to be fruitful, showing that the ethyl/methyl combination **L3** was the best (76% conv, 77:23, 71% ee) (Table 1, entry 5 vs entries 3−4). Thus, the modulation of the electronic properties of the phenolic part of the ligand was tested. We tested both electron-withdrawing and electron-donating groups in the para position of the hydroxyl group. The introduction of an electron-donating group, such as a benzyloxy goup **L6**, afforded comparable results (Table 1, entry 8), while

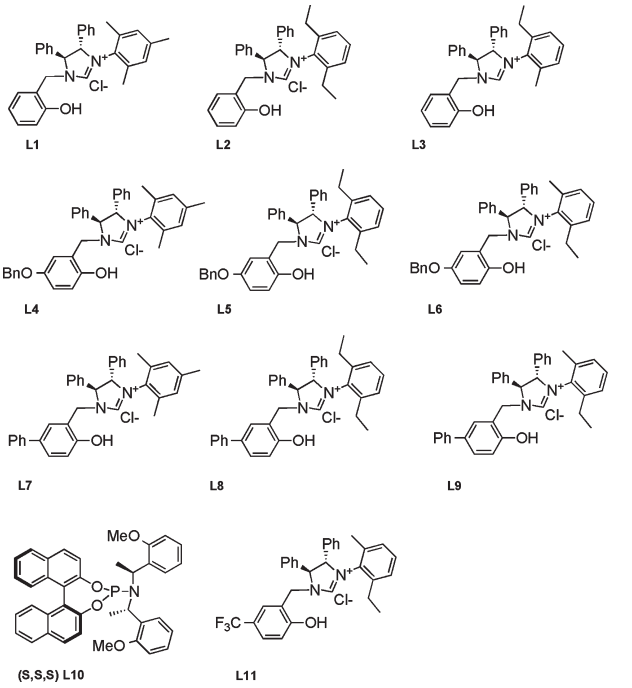
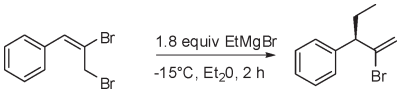


Figure 1. Chiral ligands used.

Table 1. Ligand Screening



entry	substrate	ligand	conv (%)[a]	γ:α (%)[a]	ee (%)[b]
1	*Z*	2% **L1**	8	40:60	
2	*Z*	1.5% CuTC[c], 2% **L1**	100	43:57	
3	*E*	2% **L1**	95	79:21	65
4	*E*	2% **L2**	45	71:29	55
5	*E*	2% **L3**	76	77:23	71
6	*E*	2% **L4**	97	82:18	70
7	*E*	2% **L5**	86	83:17	71
8	*E*	2% **L6**	85	77:23	68
9	*E*	2% **L7**	95	82:18	81
10	*E*	2% **L8**	99	84:16	72
11	*E*	2% **L9**	99	82:18	85
12	*E*	2% **L11**	99	75:25	60
13	*E*	1.5% CuTC[c], 2% **L1**	99	90:10	30
14	*E*	3% CuTC[c], 4% **L10**	99	92:8	65

[a] By ^{1}H (NMR). [b] By chiral SFC. [c] CuTC = copper thiophene carboxylate.

introduction of electron-withdrawing group **L11** led to lower results (Table 1, entry 12). Nevertheless, to our delight, by using the combination of the ideal blocking part and a para phenyl group **L9**, we could yield our best result (99% conv, 82:18, 85% ee) (Table 1, entry 11). We then screened the generality of our methodology toward

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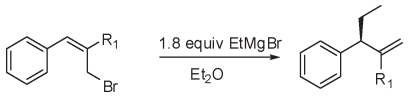
other halogens to see which one was the best compromise in terms of enantioselectivy, reactivity, selectivity, and isolated yield (Table 2). With the chloro derivative, the Cu/phosphoramidite system proved to be completely inefficient, while the NHC **L9** delivered the desired compound with 82% ee and a 80:20 γ:α selectivity, albeit with a low isolated yield of 25% (Table 2, entry 3), whereas on fluorine derivatives, both systems were unreactive (Table 2, entries 7−8). Interestingly, the vinylic iodide gave complete conversion with or without copper (Table 2, entries 5, 6). Obviously, the presence of copper increases the reactivity, as the reaction could be performed at low temperature (−78 °C). However, despite a much better gamma selectivity, the ee remains rather low, particularly when compared to the copper-free process (86% ee).

Table 2. Copper-Free AAA to Other Halogens



entry	R_1	ligand	temp (°C)	conv (%)[a]	γ:α (%)[a]	ee (%)[b]
1	Br	2% **L9**	−15	99 (70)[c]	82:18	85
2	Br	3% CuTC[d], 4% **L10**	−78	99	92:8	65
3	Cl	2% **L9**	−15	99 (25)	80:20	82
4	Cl	3% CuTC[d], 4% **L10**	−78	0		
5	I	2% **L9**	−15	99 (50)	83:17	86
6	I	3% CuTC[d], 4% **L10**	−78	99	95:5	60
7	F	2% **L9**	−15	5		
8	F	3% CuTC[d], 4% **L10**	−78	5		

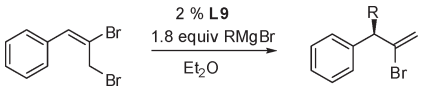
[a] By ^{1}H (NMR). [b] By chiral SFC. [c] 20% insertion of Grignard into vinylic iodine. Yield after purification on SiO_2. [d] CuTC = copper thiophene carboxylate.

Obviously the next step was the evaluation of various Grignard reagents on our model substrate (Table 3). The temperature was kept constant to −15 °C and the reaction time set to 24 h to ensure maximum conversion.

Different primary Grignard reagents could be introduced with decent to good regioselectivities on the crude product (from 73:27 to 94:6 in favor of the γ adduct) and interesting enantioselective values (73−85% ee). After purification on silica gel, isolation of pure S_N2' adducts were possible in most of the cases with decent to good yields (40−71%). We should also mention that the challenging MeMgBr could be introduced with fair results (Table 3, entry 2). In sharp contrast, secondary Grignard reagents such as isopropyl and cyclohexyl led to messy reactions. After having determined the limitation of the reaction in the scope of Grignard reagent, we began to explore the scope of substrate. A series of aliphatic and aromatic substrates were synthesized (Table 4).

The influence of the steric hindrance was studied by substitution in the ortho position of the phenyl ring next to the reactive center. We observed perfect to good regioselectivities (85:15 to 100:0 in favor of the γ adduct) and

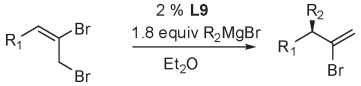
Table 3. Grignard Reagent Screen



entry	RMgBr	time (h)	conv (%)[a]	yield (%)[b]	γ:α (%)[a]	ee (%)[c]
1	Et	2	99	71	82:18 (88:12)[d]	85
2	Me	24	99	40	80:20 (93:7)	73
3	*n*Bu	24	99	55	73:27 (81:19)	78
4	*i*Amyl	24	99	60	77:23 (93:7)	81
5	Butenyl	24	99	58	84:16 (98:2)	84
6	$PhCH_2CH_2$	24	99	63	88:12 (98:2)	85
7	*i*Bu	24	99	45	94:6 (97:3)	85

[a] By ^{1}H (NMR). [b] Yield after purification on SiO_2. All reactions were performed at −15 °C. [c] By chiral SFC. [d] Ratio in parentheses is equal to regioselectivity after purification on SiO_2.

Table 4. Substrate Scope



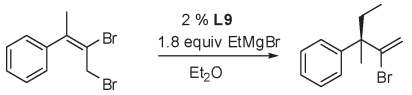
entry	R_1	R_2	conv (%)[a] (yield %)[b]	γ:α (%)[a]	ee (%)[c]
1	*o*ClPh	Et	93 (54)	88:12 (89:11)[d]	80
2	*o*MePh	Et	88 (60)	100:0	93
3	*p*MePh	Et	99 (58)	80:20 (86:14)	86
4	*p*ClPh	Et	99 (53)	85.15 (92:8)	85
5	Cy	Et	99 (61)	100:0	88
6	*t*Bu	$PhCH_2CH_2$	70 (50)	100:0	93
7	*i*Pr	$PhCH_2CH_2$	99 (70)	95:5 (100:0)	69
8	Me	$PhCH_2CH_2$	99 (65)	90:10 (100:0)	11

[a] By ^{1}H (NMR). [b] Yield after purification on SiO_2. All reactions were performed at −15 °C. [c] By chiral GC or SFC. [d] Ratio in parentheses is equal to regioselectivity after purification on SiO_2.

good to excellent enantioselectivities (80−93% ee), showing that the steric hindrance is well tolerated (Table 4, entries 1−2). Next we probed the influence of electronic properties by substitution in the para position of the phenyl ring. We were able to get results (80:20 to 85:15 in favor of the γ adduct, 85−86% ee) comparable to the simple phenyl ring (Table 4, entries 3−4). We focused next on the aliphatic substrates. On those substrates, a very sharp trend of steric hindrance was noticed. Excellent results were obtained using sterically demanding substrates as cyclohexyl or *tert*-butyl moieties (100:0 in favor of the γ adduct and 88−93% ee) (Table 4, entries 5−6). By decreasing gradually the steric hindrance to isopropyl or to a methyl group, this led to a dramatic decrease of enantioselectivity (69% ee for isopropyl, 11% ee for methyl) while keeping high levels of regioselectivty (95:5, 90:10 in favor of the γ adduct) (Table 4, entries 7−8). On quaternary

centers, the reaction proceeded sluggishly, and addition of copper salt was beneficial to the catalytic system in terms of conversion, though affording modest enantioselectivity, showing the limitation of our methodology at the present time of our research. The further development of a more active catalyst could afford high enantioselectivity, as a sharp correlation of temperature/enantioselectivity was observed (Table 5, entry 1 vs entry 2).

Table 5. Application to Quaternary Centers



entry	ligand	temp (°C)	time (h)	conv (%)[a] (yield %)[b]	γ:α (%)[a]	ee (%)[c]
1	2% **L9**	−5	14	99 (50)	82:18	60
2	2% **L9**	−15	14	20	90:10	79
3	2% CuTC, 3% **L9**	−15	14	100 (60)	90:10	65

[a] By ^{1}H (NMR). [b] Yield after purification on SiO_2. [c] By chiral SFC.

First we propose herein, as an application of our system, the extension of the methodology developed by Woodward (Scheme 2).[7] Woodward reported the AAA to Baylis−Hillman derived substrates using amine catalysts. The addition of diethyl zinc to such substrate was possible, with ee values ranging from 76 to 90% ee. However, because of the synthetic sequence, aliphatic substrates cannot be accessed, and the system was limited to a single nuleophile (diethyl zinc). With the present results, we could extend this methodology to several other carbonyl derivatives (aldehyde, acid) that could be easily obtained, depending on the electrophile used, with a rich scope of substrates and nucleophiles. Second, we propose the synthesis of 1,1-disubstituted silane derivatives. This intermediate represents itself a new class of substrates, which has not been reported yet by AAA. Importantly, this synthon is a versatile intermediate, as it can be used in the Hiyama coupling reaction. Last but not least is the use of our vinylic bromide as coupling partner in Suzuki and Sonogashira reactions. An alkyne containing a TMS unit could be introduced in good yield using the Sonogashira reaction. We managed also to enter a large panel of aryl or heteroaryl moieties using a Suzuki coupling reaction. The presence of chiral synthons containing aryls or heteroaryls in vinylic positions have never been reported in the literature.

To conclude, we have disclosed a class of substrates where a copper-free system using bidendate NHC ligand

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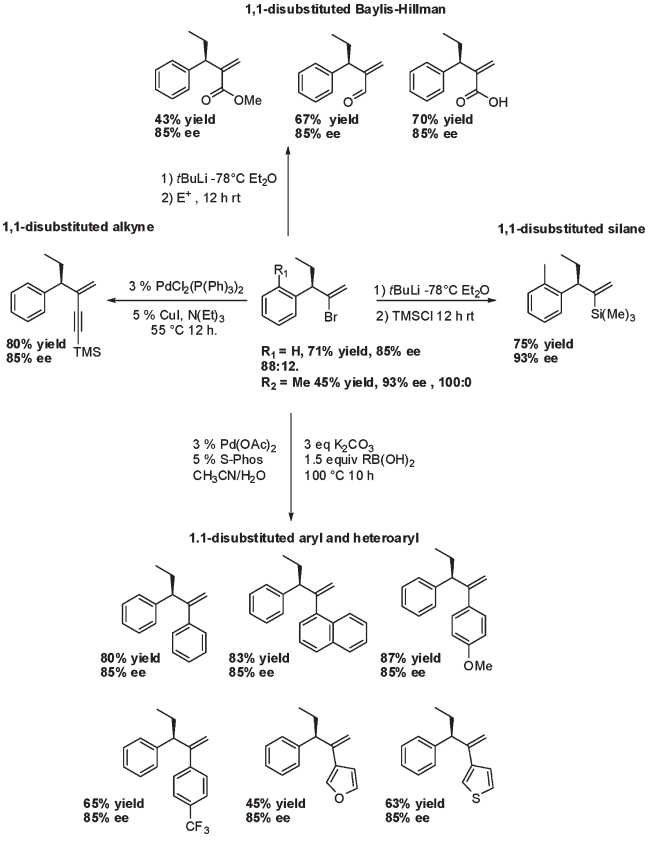
Scheme 2. Application toward New Classes of Substrates



and Grignard reagents led to interesting results in terms of enantioselectivity and regioselectivity. The substrate scope is large, and more importantly, the products display an unprecedented potential of further transformations. The extension to new classes of Baylis−Hillman derived substrates, a new family of silane derivatives, and a large panel of 1,1-disubstituted aryls and heteroaryls has been disclosed. With a single catalytic product in hand, several series of nonreported compounds could be synthetized, in a single step transformation without erosion of the enantioselectivity.

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Supporting Information Available. Experimental procedures, NMR spectra, and chiral separations for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.