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Copper-catalyzed asymmetric conjugate addition of Grignard reagents to 1-(*N,N*-diisopropylcarbamoyloxy)-1-tosyl-1-alkenes

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ABSTRACT

A copper-catalyzed conjugate addition of Grignard reagents to 1-(*N,N*-diisopropylcarbamoyloxy)-1-tosyl-1-alkenes led to 1-(*N,N*-diisopropylcarbamoyloxy)-1-tosyl-2-branched alkanes. Various copper ligands were screened for this reaction. From certain substrates and allylmagnesium bromide, several Josiphos ligands gave low to moderate asymmetric inductions, along with good diastereoselectivity. The stereochemistry of the 1-(*N,N*-diisopropylcarbamoyloxy)-1-tosyl-2-branched alkanes from this reaction was assigned by comparison with the same products from another synthetic route using chiral pool synthesis and stereoselective lithiation methods.

1. Introduction

We have recently introduced 1-(*N,N*-diisopropylcarbamoyloxy)-1-tosyl-1-alkenes **1** as useful a^2d^1 synthons via tandem umpolung.[1] This was achieved by the copper-catalyzed addition of Grignard reagents followed by addition/migration/elimination with various carbonyl compounds. This method formally installs a carbanion unit and a carbonyl unit, respectively, onto the α-carbon and the carbonyl center of an aldehyde to give α,α′-branched-α′-oxygenated ketones **4**. Additionally, we described therein that the magnesiated intermediate **2** can be hydrolyzed directly to give the useful synthetic intermediate **3** (Scheme 1).

The first addition is presumably the conjugate addition of the Grignard reagent to a less activated alkene resulting from the contradictorily operating substituents on C-1, and this can be synthetically important. Although catalytic nucleophilic asymmetric conjugate addition (ACA) on activated substrates such as α,β-unsaturated carbonyl derivatives,[2] and the recently reported copper-catalyzed ACA on vinyl sulfone substrates by organozinc[3] and Grignard reagents[4] have achieved great success catalytic nucleophilic ACA on less activated alkene substrates such as 1-(*N,N*-diisopropylcarbamoyloxy)-1-tosyl-1-alkenes have been rarely explored,[5] probably due to reactivity and diastereoselectivity issues.

Herein, we report our preliminary investigations on the copper-catalyzed ACA on 1-(*N,N*-diisopropylcarbamoyloxy)-1-tosyl-1-alkenes by Grignard reagents, which leads to enantioenriched synthetic intermediate **3**.

2. Results and discussion

The model reactions subjected to the catalytic ACA were reported in a previous paper[1] and are illustrated in Table 1. Compounds **5a**,**b** as *E/Z* isomers were chosen as substrates; isopropenylmagnesium bromide and allylmagnesium bromide were used as carbanion sources. Without chiral ligands, compounds **6** and **7** were obtained in good yields.

To understand the proposed catalytic ACA, we designed a new synthetic pathway to assign all the possible stereoisomers of products **6** and **7** (Scheme 2 and Table 2). Commercially available enantiomerically pure (*S*)-phenyloxirane was reacted with Grignard reagents to give the α-branched alcohols **8** and **9**,[6] which were condensed with *N,N*-diisopropylcarbamoyl (Cb) chloride to give carbamates **10** and **11**. According to the stereoselective deprotonation methods[7] established in our group, compounds **10** and **11** were treated with TMEDA/*s*-BuLi or (−)-sparteine/*s*-BuLi, respectively, and then quenched by TsF to produce enantioenriched products **6** and **7**. When compound **10** was treated with TMEDA/*s*-BuLi, substituents on C-2 only slightly affected the newly produced stereogenic center on C-1.[8] Conversely, with the same TMEDA/*s*-BuLi system, substitutions on C-2 of compound **11** produced good internal asymmetric induction on C-1.[9] When the (−)-sparteine/*s*-BuLi system was applied, moderate to good external asymmetric inductions were achieved for both substrates **10** and **11**. With a baseline resolution on chiral-HPLC, the absolute stereochemistry of the four possible stereoisomers of products **6** and **7** can be deduced according to the following materials: (1) the two diastereomeric pairs (each contains a couple of enantiomers) were identified by the first

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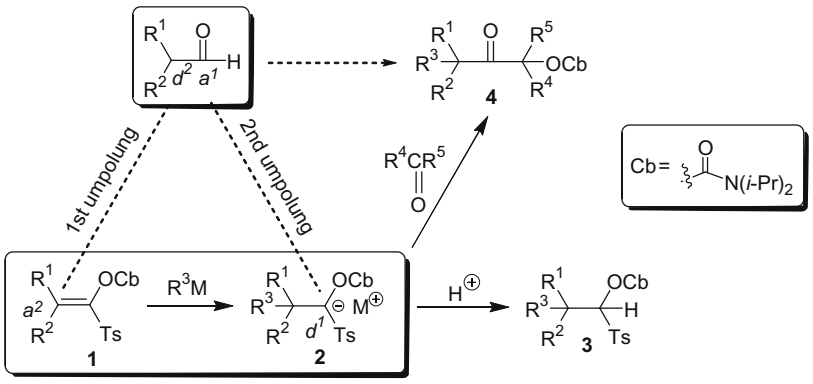
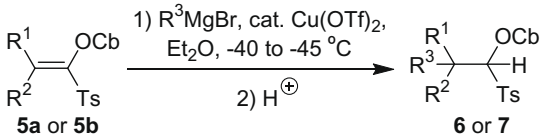


Scheme 1. 1-(*N*,*N*-Diisopropylcarbamoyloxy)-1-tosyl-1-alkenes **1** are a^2d^1 synthons via tandem umpolung. With this protocol, compound **3** can also be produced as a useful synthetic intermediate.

addition in Table 1 with moderate diastereoselectivity; two peaks of the same integration should be a couple of enantiomers; (2) in each enantiomeric pair, the configuration at C-2 was determined by the (*S*)-phenyloxirane starting material; (3) in each enantiomeric pair, the configuration at C-1 was then deduced from (a) the known enantioselective deprotonation with (−)-sparteine/*s*-BuLi system,[7] (b) the diastereoselective deprotonation on substrates **11**, analogous to 2-phenylpropyl 2,2,4,4-tetramethyl-1,3-oxazolidine-3-carboxylate system,[7] and (c) the further stereospecific nucleophilic substitution from the lithiated **10** or **11**.[7]

Table 1
Addition of Grignard reagents to 1-(*N*,*N*-diisopropylcarbamoyloxy)-1-tosyl-1-alkenes[1]



No.	Edduct/product	R^1	R^2	R^3	Yield (%)	dr
1	**5a**/**6**	Ph	H	Isopropenyl	84	0.42
2	**5b**/**6**	H	Ph	Isopropenyl	92	2.5
3	**5a**/**7**	Ph	H	Allyl	95	1.0
4	**5b**/**7**	H	Ph	Allyl	84	0.95

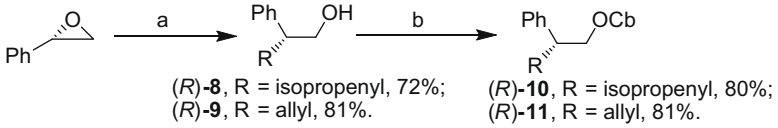
To investigate the catalytic ACA on the model reactions in Table 1, typical copper ligands **12**,[10] **13**,[11] **14**,[12] **15**,[13] **16**,[11] **17**,[14] **18**,[15] **19**,[16] and **20**[11] were screened (Fig. 1).

Some ligands were applied to the addition reaction using an isopropenyl Grignard reagent and the results are shown in Table 3. The initial two experiments (entries 1 and 2) were started from compound **5a** with NHC ligand **12** or Josiphos ligand **13**. Under typical reaction conditions, yields much lower (although a good dr was observed in entry 1) than those obtained through the model reaction without a ligand were obtained. Under the same reaction conditions, the yields of the later entries (entries 3–7) using substrate **5b** are higher than those obtained using substrate **5a** (but still lower than those of the original model reaction). Entry 7 gave a noticeable er, however its yield was again very low. It was felt that these ligands decelerate the reaction significantly; hence the more reactive allylmagnesium bromide was used to test the ACA.

The screening results for the conversion from compounds **5a**,**b** to compound **7** are listed in Table 4. Starting from compound **5a** and allylmagnesium bromide, although no significant er can be observed with ligands **14** and **16**, better yields were obtained (entries 1 and 2). We then turned our focus to compound **5b** as the starting material.[17] It was initially observed that Josiphos **16** led to low er in Et_2O at −30 °C (entries 3 and 4), while Taniaphos **17** failed to induce any noticeable er for the model reaction (entry 5). With Josiphos **16**, we further observed that cooling the reaction mixture and using DCM instead of Et_2O or TBME as a solvent induced higher er and good dr (entries 7, 11, and 12). NHC ligand **12** and oxazoline–phosphine ligand **18** did not induce any noticeable er (entries 8 and 9). Bisoxazoline ligand **15** gave poor yield due to significant side product formation (entry 10). Our biphenol-based phosphite **19** failed to produce a useful er, probably due to its instability[18] with the Grignard reagent (entry 13). Josiphos **20**, with the inverted substitution on two phosphorus centers, led to slightly lower er as did Josiphos **16** (entry 15). Interestingly, Josiphos **13**, with only a change from a diphenylphosphino group to dicyclohexylphosphino group based on Josiphos **16** or **19**, inverts the enantioselectivity completely and leads to highest er (26.0:74.0, with a corresponding ee of 48%) and dr (98.8:1.2) in all the examples (entries 15–17). In general, the counterions from the copper sources used in this work did not cause significant change of the asymmetric induction (entries 6, 16, and 17).

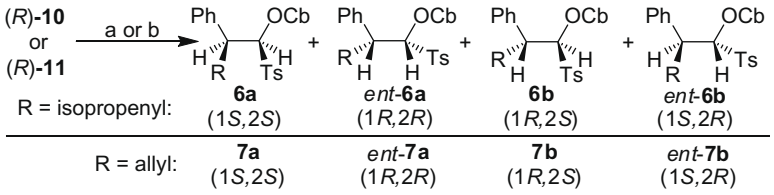
3. Conclusions

From the above results, it may be concluded that most of the frequently used copper ligands decelerate the addition of magnesium organocuprate to 1-(*N*,*N*-diisopropylcarbamoyloxy)-1-tosyl-1-alkenes. Substrate **5a** demonstrated low reactivity toward additions by ligand-incorporated magnesium organocuprates, while on the other hand, it gave practically no er in various tests. Substrate **5b**, along with allylmagnesium bromide, was able to give low to moderate er with several Josiphos ligands, but not with other typical copper ligands, including Taniaphos and BINAP.



Scheme 2. Reagents and conditions: (a) Grignard reagent, CuBr·Me_2S, Et_2O; and (b) NaH, CbCl, THF, 90 °C.

Table 2
Stereoselective deprotonation of compounds **10** and **11** and stereospecific reaction with TsF led to compounds **6** and **7**



No.	Edduct	Product distribution	Yield (%)	er (*R*/*S*, on C1)[c]	er (*R*/*S*, on C2)[c]
1[a]	(*R*)-**10**	4.4:52.7:3.8:39.1 (**6a**:*ent*-**6a**:**6b**:*ent*-**6b**)	69	56.5:43.5	91.8:8.2
2[b]	(*R*)-**10**	7.8:12.2:0.5:79.5 (**6a**:*ent*-**6a**:**6b**:*ent*-**6b**)	49	12.7:87.3	91.7:8.3
3[a]	(*R*)-**11**	2.8:88.8:0:8.4 (**7a**:*ent*-**7a**:**7b**:*ent*-**7b**)	61	88.8:11.2	97.2:2.8
4[b]	(*R*)-**11**	3.7:14.9:0:81.5 (**7a**:*ent*-**7a**:**7b**:*ent*-**7b**)	38	14.9:85.1	96.3:3.7

[a] Conditions: TMEDA, *s*-BuLi, Et_2O, −78 °C, then TsF.
[b] Conditions: (−)-sparteine, *s*-BuLi, Et_2O, −78 °C, then TsF.
[c] Er was determined by chiral HPLC on a Eurocel-01 chiral column.

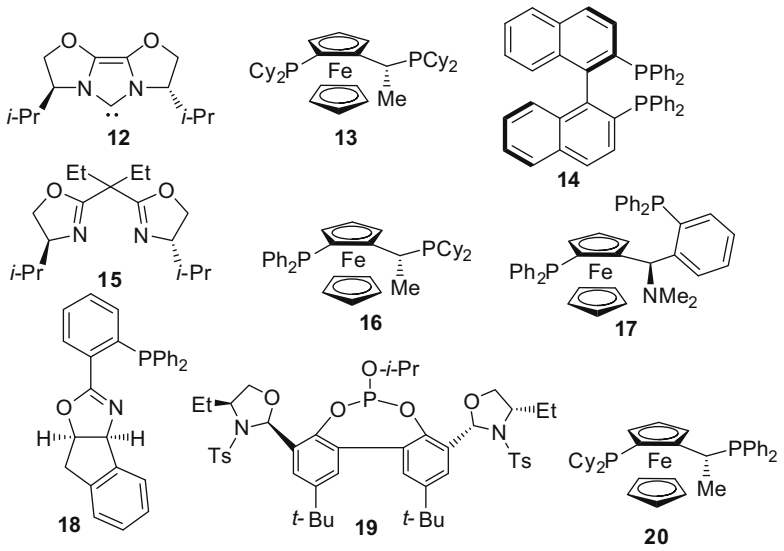
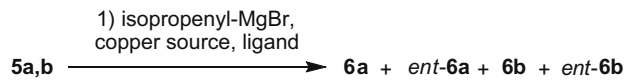


Figure 1. Ligands screened in this work.

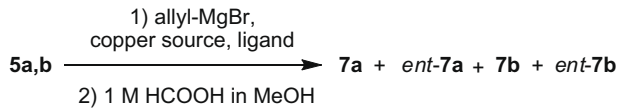
Table 3
The ACA from compounds **5a**,**b** to **6**[a]



No	Edduct	Copper/ligand	*T* (°C)	Yield[b,c] (%)	Product distribution:[b] **6a**:*ent*-**6a**:**6b**:*ent*-**6b**	er (on C-2)[b,d]	dr[b,e]
1	**5a**	$Cu(OTf)_2$/**12**	−45	21	44.6:55.4:0:0	44.6:55.4	>99:1
2	**5a**	$Cu(OTf)_2$/**13**	−45	<5	n.a.	n.a.	n.a.
3	**5b**	CuCl/**14**	−30	70	15.8:17.1:33.8:33.3	49.6:50.4	32.9:67.1
4	**5b**	CuCl/**15**	−30	83	27.9:25.1:24.7:22.3	52.6:47.4	53.0:47.0
5	**5b**	$Cu(OTf)_2$/**12**	−45	36	8.5:8.0:38.9:44.6	47.4:52.6	16.5:83.5
6	**5b**	CuCl/**13**	−30	79	7.5:8.3:44.6:39.6	52.1:47.9	15.8:84.2
7	**5b**	CuCl/**16**	−20	25	39.2:42.0:0:18.8	39.2:60.8	81.2:18.8

[a] See Section 4.5, part (a) for the general procedure of entries 2–7, part (b) for that of entry 1; diethyl ether was used as the solvent for all these reactions.
[b] Yields, er, and dr were determined by HPLC on a Eurocel-01 chiral column.
[c] In the low yield cases, a large amount of unreacted starting material was found by HPLC or GC analysis.
[d] The er ratio is for *S*/*R*.
[e] The dr ratio is for (**6a** + *ent*-**6a**)/(**6b** + *ent*-**6b**).

Table 4
The ACA from compounds **5a**,**b** to **7**[a]



No.	Edduct	Solvent[b]	Copper/ligand	T (°C)	Yield[c,d] (%)	Product distribution:[c] **7a**:*ent*-**7a**:**7b**:*ent*-**7b**	er on C-2[c,e]	dr[c,f]
1	**5a**	Et_2O	CuCl/**14**	−30	63	35.9:34.2:14.8:15.1	50.7:49.3	70.1:29.9
2	**5a**	Et_2O	CuCl/**16**	−60	68	40.0:39.8:6.8:13.4	46.8:53.2	79.8:20.2
3	**5b**	Et_2O	CuCl/**16**	−30	51	43.0:23.5:17.8:15.7	60.8:39.2	66.5:33.5
4[g]	**5b**	Et_2O	CuCl/**16**	−30	46	40.0:24.5:17.2:18.3	57.2:42.8	64.5:35.5
5	**5b**	Et_2O	CuCl/**17**	−60	70	21.3:22.9:30.0:27.8	51.3:48.7	44.2:55.8
6	**5b**	Et_2O	$(CuOTf)_2$·Toluene/**16**	−60	63	45.7:21.0:17.9:15.4	63.6:36.4	66.7:33.3
7	**5b**	Et_2O	CuCl/**16**	−78	57	53.0:23.8:12.7:10.5	65.7:34.3	76.8:23.2
8	**5b**	Et_2O	$Cu(OTf)_2$/**12**	−78	49	24.6:25.0:25.0:25.4	49.6:50.4	49.6:50.4
9	**5b**	Et_2O	CuCl/**18**	−78	60	27.9:29.5:20.8:21.8	48.7:51.3	57.4:42.6
10	**5b**	Et_2O	CuCl/**15**	−78	21	64.4:15.6:5.5:14.5	69.9:30.1	80.0:20.0
11	**5b**	TBME	CuCl/**16**	−78	51	50.0:25.5:13.5:11.0	63.5:36.5	75.5:24.5
12	**5b**	DCM	CuCl/**16**	−78	70	67.4:27.6:3.3:1.7	70.7:29.3	95.0:5.0
13	**5b**	DCM	CuCl/**19**	−78	38	10.0:12.4:39.8:37.8	49.8:50.2	22.4:77.6
14	**5b**	DCM	CuCl/**20**	−78	80	58.2:32.1:5.2:4.5	63.4:36.6	90.3:9.7
15	**5b**	DCM	CuCl/**13**	−78	91	25.5:73.3:0.52:0.63	26.0:74.0	98.8:1.2
16	**5b**	DCM	CuBr·DMS/**13**	−78	Quant.	27.3:71.0:0.7:1.0	28.0:72.0	98.3:1.7
17	**5b**	DCM	CuBr/**13**	−78	Quant.	27.0:71.0:1.1:0.9	28.1:71.9	98.0:2.0

[a] See Section 4.5, part (a) for the general procedure of entries 1–3, 5–7, and 9–17, part (b) for that of entry 8.
[b] It is essential to avoid using THF as solvent for a useful er.
[c] Yield, er, and dr were determined by HPLC on a Eurocel-01 chiral column.
[d] In the low yield cases, a large amount of unreacted starting material was found by HPLC or GC analysis, except for entry 10, where the low yield was accompanied by a large amount of unknown side products presented on HPLC.
[e] The er ratio is for *S*/*R*.
[f] The dr ratio is for (**7a** + *ent*-**7a**)/(**7b** + *ent*-**7b**).
[g] See Section 4.5, part (c) for the reversed addition procedure of entry 4, where the substrate **5b** was added slowly into the magnesium cuprate solution.

Furthermore, DCM is a good solvent for this addition concerning the improved er and good dr. Also, different couterions from the copper source used in this work had only little effect on the asymmetric induction, when Grignard bromides were used. These observations may be compared with the results from (1) ACAs of α,β-unsaturated carbonyl derivatives with magnesium cuprates,[2a] and (2) ACAs of vinyl sulfones with zinc cuprates[3] or magnesium cuprates,[4] for interesting common or different characters.

In conclusion, we screened various typical copper ligands for the copper-catalyzed ACAs of Grignard reagent to 1-(*N*,*N*-diisopropylcarbamoyloxy)-1-tosyl-1-alkenes, which led to 1-(*N*,*N*-diisopropylcarbamoyloxy)-1-tosyl-2-branched alkanes. From substrate **5b** and allylmagnesium bromide, several Josiphos ligands were found to induce low to moderate er of the desired addition product. The stereochemistry of 1-(*N*,*N*-diisopropylcarbamoyloxy)-1-tosyl-2-branched alkanes from this reaction was assigned by comparison with the same products from another synthetic route using chiral pool synthesis and stereoselective lithiation methods developed in our group.

4. Experimental

4.1. General

All solvents were dried and purified prior to use: Et_2O was distilled from sodium with benzophenone as indicator, THF was distilled from potassium, and CH_2Cl_2 was distilled from CaH_2. Solutions of *s*-BuLi (purchased from Sigma–Aldrich) were filtered through a pad of Celite under argon in order to remove any precipitate and were stored in a freezer (−30 °C). The content of *s*-BuLi was determined by titration. 1,2-Bis(dimethylamino)ethane (TMEDA) was distilled over CaH_2 and stored under Ar. Isopropenylmagnesium bromide diethyl ether solution was prepared from isopropenyl bromide and magnesium and titrated before use. Allyl magnesium bromide is commercially available and was titrated before use. All other commercially available reagents were used as received. Reactions at −78 °C were performed in a dry ice/acetone bath. For other temperatures below 0 °C, a *Julabo* FT902 cryostat and an acetone bath were used. All moisture/air-sensitive reactions were performed under Ar (ca. +0.3 bar gauge) in 500–600 °C/vacuum-dried glassware sealed with a rubber septum. Medium pressure liquid chromatography (MPLC) was performed on *Merck* 60 silica gel (40–60 μm, 230–400 mesh ASTM), and monitored by thin layer chromatography (TLC) on *Merck* 60 F254 TLC-plates. NMR data were collected on a *Bruker* AV 300, a AV 400, a ARX 400, a *Varian* Inova 500 or a Unity Plus 600. ^1H and ^{13}C NMR data were calibrated relative to the residual $CHCl_3$ peak (7.26 ppm for ^1H NMR and 77.0 ppm for ^{13}C NMR). IR data were collected on a *Varian* 3100 Excalibur Series with *Specac* Golden Gate Single Reflection ATR. Mass data were collected on a *Bruker* MicroTof (ESI). Optical rotation data were collected on a *Perkin Elmer* 341 or 241 at ambient temperature (ca. 20–25 °C). Elemental analyses were performed on an *Elementar-Analysensysteme* Vario EL III. GC data were collected on a *Agilent* 6890 with a 30 m × 0.32 mm HP-5 column (GC condition: 1.5 mL × min^{-1} H_2; starting at 50 °C, 10 °C × min^{-1} to 300 °C, 15 min at 300 °C) HPLC data were collected with a *Knauer* Smartline PDA detector 2600, a Pump 1000, an Autosampler 3900, and a Manager 5000.

4.2. General procedure for ring opening of (*S*)-phenyloxirane

The CuBr·DMS complex (100 mg, 0.49 mmol) was suspended in 20 mL of diethyl ether at −78 °C. A diethyl ether solution of Grignard reagent (1.0 mmol) was added dropwise to the above suspension. The resulting mixture was stirred and warmed gradually to −30 °C, maintained at −30 °C for 10 min, and cooled back to −78 °C. To the above mixture, (*S*)-phenyloxirane (neat, 120 mg, 1 mmol) was added dropwise. The resulting suspension was again

warmed to −20 °C and stirred for 4 h. The reaction was quenched by addition of satd aq NH_4Cl. The organic phase was separated and the water phase was washed several times with diethyl ether. The combined organic layers were passed through a silica gel plug and evaporated. The residue was purified by MPLC (*n*-pentane/diethyl ether = 20:1 to 10:1 to 5:1 to 1:1) to give the product **8** or **9**.

4.2.1. (*R*)-3-Methyl-2-phenylbut-3-en-1-ol 8

From (*S*)-phenyloxirane (120 mg, 1.0 mmol), compound **8** (117 mg, 0.72 mmol, 72%) was obtained as a colorless oil. $[\alpha]_D = -55.3$ (*c* 1, $CHCl_3$). GC and ^1H NMR match the reported data;[1] HRMS matches the calculated value.

4.2.2. (*R*)-2-Phenylpent-4-en-1-ol 9

From (*S*)-phenyloxirane (120 mg, 1.0 mmol), compound **9** (131 mg, 0.81 mmol, 81%) was obtained as a colorless oil. $[\alpha]_D = +6.0$ (*c* 1, $CHCl_3$). GC and ^1H NMR match the reported data;[1] HRMS matches the calculated value.

4.3. General procedure for condensation of alcohols 8 and 9 and CbCl

A solution of alcohol **8** or **9** (100 mg, 0.62 mmol) in 2 mL of THF was added dropwise into a mixture of NaH (60% in oil, 37 mg, 0.93 mmol, 1.5 equiv) and 1 mL of THF at rt. The suspension was then stirred at rt for 30 min before CbCl (152 mg, 0.93 mmol, 1.5 equiv) was added portionwise. The resulting mixture was then heated in a sealed tube at 90 °C overnight (pressure will build up upon scaling up). The reaction was quenched by the addition of satd aq NH_4Cl. The organic phase was then separated and the water phase was washed several times with diethyl ether. Combined organic layers were passed through a silica gel plug and evaporated. The residue was purified by MPLC (*n*-pentane/diethyl ether = 30:1 to 20:1 to 10:1 to 5:1) to yield product **10** or **11**.

4.3.1. (*R*)-3-Methyl-2-phenylbut-3-enyl *N,N*-diisopropylcarbamate 10

From compound **8** (100 mg, 0.62 mmol), compound **10** (145 mg, 0.50 mmol, 81%), was obtained as a colorless oil. $R_f = 0.50$ (ethyl acetate/cyclohexane = 1:2). $t_R = 16.3$ min (HP-5). $[\alpha]_D = -36.0$ (*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ/ppm 7.27–7.12 (m, 5H, Ph), 4.86 (pseudo-s, 2H, CH_2=), 4.45–4.30 (m, 2H, CbO–CH_2), 4.08–3.50 (br s, 2H, Cb), 3.57 (t, *J* = 7.6 Hz, 1H, Ph(isopropenyl)CH), 1.58 (s, 3H, CH_3), 1.13–1.04 (m, 12H, Cb). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm 157.6 (C=O), 144.80 (Me–*C*=), 140.42 (Ph), 128.32 (2C, Ph), 128.15 (2C, Ph), 126.68 (Ph), 111.69 (CH_2=), 66.13 (*C*H_2–OCb), 51.62 (CH), 45.51 (2C, Cb), 21.66 (4C, Cb), 20.75 (CH_3). FTIR ($CHCl_3$ cast film microscope) ν 3083 (m), 3065 (m), 3029 (m), 2969 (s), 2935 (m), 2879 (m), 1687 (s), 1647 (m), 1437 (s), 1368 (s), 1308 (s), 1290 (s), 1134 (s), 1060 (s), 895 (s), 701 (s). HRMS (ESI+) calcd for $C_{18}H_{27}NO_2Na^+$ 312.1934, found 312.1924. Anal. Calcd for $C_{18}H_{27}NO_2$ (289.41): C, 74.70; H, 9.40; N, 4.84. Found: C, 74.33; H, 9.34; N, 4.66.

4.3.2. (*R*)-2-Phenylpent-4-enyl *N,N*-diisopropylcarbamate 11

From compound **9** (100 mg, 0.62 mmol), compound **11** (145 mg, 0.50 mmol, 81%), was obtained as a colorless oil. $R_f = 0.51$ (ethyl acetate/cyclohexane = 1:2). $t_R = 16.2$ min (HP-5). $[\alpha]_D = +2.7$ (*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ/ppm 7.23–7.10 (m, 5H, Ph), 5.68–5.57 (m, 1H, CH=), 4.96–4.87 (m, 2H, CH_2=), 4.26 (dd, *J* = 6.3 Hz, 10.8 Hz, 1H, CH_2–O), 4.11 (dd, *J* = 8.1 Hz, 10.8 Hz, 1H, CH_2–OCb), 3.93 (br s, 1H, Cb), 3.56 (br s, 1H, Cb), 3.03–2.96 (m, 1H, CH-Ph), 2.45–2.30 (m, 2H, CH_2), 1.22–0.80 (s, 12H, Cb). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm 155.51 (C=O), 141.96 (Ph), 135.90 (CH=), 128.31 (2C, Ph), 127.95 (2C, Ph), 126.56 (Ph), 116.56 (CH_2=), 68.18 (CH_2–OCb), 46.29 (Cb), 45.25 (Cb), 45.09 (CH-Ph), 37.23 (CH_2), 20.86 (2C, Cb), 20.78 (2C, Cb). FTIR ($CHCl_3$ cast film microscope) ν 3078 (m), 3064 (m), 3030 (m), 2998 (m), 2970 (s), 2933 (m), 2875 (m), 1688 (s), 1642 (m), 1436 (s), 1368 (s), 1308 (s), 1290 (s), 1218 (s), 1134 (s), 1068 (s), 701 (s), 632 (s). HRMS (ESI+) calcd for $C_{18}H_{27}NO_2Na^+$ 312.1934, found 312.1934. Anal. Calcd for $C_{18}H_{27}NO_2$ (289.41): C, 74.70; H, 9.40; N, 4.84. Found: C, 74.52; H, 9.40; N, 4.72.

4.4. General procedure for the stereoselective deprotonation of compounds 10 and 11 and the following quench by TsF leading to compounds 6 and 7

At first, *s*-BuLi (0.16 mL, 1.28 M in *n*-hexane, 0.21 mmol, 1.2 equiv) was added dropwise to a solution of diamine (TMEDA or (−)-sparteine, 0.21 mmol, 1.2 equiv) in 0.5 mL diethyl ether at −78 °C. To the above mixture, a solution of carbamate **10** or **11** (50 mg, 0.17 mmol, 1 equiv) in diethyl ether (1 mL) was added dropwise. The resulting mixture was then stirred at −78 °C for 8 h (for substrate **10**) or 3 h (for substrate **11**). A solution of TsF (44 mg, 0.26 mmol, 1.5 equiv) in diethyl ether (1 mL) was added dropwise into the mixture and the stirring was continued for 2 h at −78 °C. The reaction was quenched with a solution of formic acid in MeOH, followed by addition of satd aq NH_4Cl. The organic phase was then separated and the water phase was washed several times with diethyl ether. Combined organic layers were washed with satd aq NH_4Cl, satd aq $NaHCO_3$, and brine in turn and evaporated to dryness. The residue was purified by MPLC (*n*-pentane/diethyl ether = 20:1 to 10:1 to 5:1 to 1:1) to yield the product **6** or **7**.

4.4.1. 3-Methyl-2-phenyl-1-tosyl-but-3-enyl *N,N*-diisopropylcarbamate 6

From carbamate **10** (50 mg, 0.17 mmol), with TMEDA/*s*-BuLi system, compound **6** (53 mg, 0.12 mmol, 69%) was obtained, whose GC and ^1H NMR match the reported data (from the diastereomeric mixture);[1] HRMS matches the calculated value; er on C1 (*R*:*S*): 56.5:43.5; er on C2 (*R*:*S*): 91.8:8.2; $[\alpha]_D = +6.7$ (*c* 1, $CHCl_3$). From carbamate **10** (50 mg, 0.17 mmol), with (−)-sparteine/*s*-BuLi system, compound **6** (38 mg, 0.085 mmol, 49%) was obtained, whose GC and ^1H NMR match the reported data (from the diastereomeric mixture);[1] HRMS matches the calculated value; er on C1 (*R*:*S*): 12.7:87.3; er on C2 (*R*:*S*): 91.7:8.3; $[\alpha]_D = -35.5$ (*c* 1, $CHCl_3$). The following interpretation of the analytical data of compound **6**[1] can then be derived: $t_R = 24.0$ min (**6a** and *ent*-**6a**), 24.2 min (**6b** and *ent*-**6b**) (HP-5); Chiral HPLC: Eurocel 01 (5 μm, 250 × 4.6 mm), *i*-PrOH/*n*-hexane: 1:150, 37 min (**6a**), 41 min (*ent*-**6a**); 51 min (**6b**), 66 min (*ent*-**6b**). NMR of (**6a** and *ent*-**6a**): ^1H NMR (400 MHz, $CDCl_3$): δ/ppm 7.73 (d, *J* = 8.3 Hz, 2H, Ts), 7.22 (d, *J* = 7.8 Hz, 2H, Ts), 7.19–7.13 (m, 5H, Ph), 6.43 (d, *J* = 10.3 Hz, 1H, Ts(OCb)CH), 5.18 (s, 1H, CH_2=), 4.89 (s, 1H, CH_2=), 4.24 (d, *J* = 10.3 Hz, 1H, Ph(isopropenyl)CH), 3.65–3.60 (m, 1H, Cb), 3.18–3.15 (m, 1H, Cb), 2.33 (s, 3H, Ts), 1.71 (s, 3H, CH_3), 0.89 (d, *J* = 6.8 Hz, 3H, Cb), 0.75 (d, *J* = 6.8 Hz, 3H, Cb), 0.69 (d, *J* = 6.8, 3H, Cb), 0.54 (d, *J* = 6.8 Hz, 3H, Cb); ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm 149.79 (C=O), 143.77 (Ts-), 141.57 (Me–*C*=), 137.63 (Ph), 133.39 (Ts), 128.73 (2C, Ts), 128.21 (2C, Ts), 127.42 (Ph), 127.26 (Ph), 127.22 (Ph), 126.37 (Ph), 125.86 (Ph), 113.61 (CH_2=), 83.57 (Ts(OCb)*C*H), 51.47 (Ph(isopropenyl)*C*H), 45.44 (Cb), 44.41 (Cb), 20.57 (Ts), 19.26 (Cb), 19.16 (CH_3), 18.98 (Cb), 18.90 (Cb), 18.78 (Cb); NMR of (**6b** and *ent*-**6b**): ^1H NMR (400 MHz, $CDCl_3$): δ/ppm 7.46 (d, *J* = 8.3 Hz, 2H, Ts), 7.08 (d, *J* = 8.1 Hz, 2H, Ts), 7.19–7.13 (m, 5H, Ph), 6.39 (d, *J* = 10.7 Hz, 1H, Ts(OCb)CH), 4.91(s, 1H, CH_2=), 4.75 (s, 1H, CH_2=), 4.12 (d, *J* = 10.7 Hz, 1H, Ph(isopropenyl)CH), 4.03–3.93 (m, 1H, Cb), 3.58–3.51 (m, 1H, Cb), 2.29 (s, 3H, Ts), 1.57 (s, 3H, CH_3), 0.95 (d, *J* = 6.8 Hz, 3H, Cb), 1.10–1.06

(m, 9H, Cb-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm 150.82 (C=O), 143.28 (Ts), 142.73 (Me–*C*=), 136.02 (Ph), 133.93 (Ts), 128.29 (2C, Ts), 128.04 (2C, Ts), 127.42 (Ph), 127.26 (Ph), 127.22 (Ph), 126.37 (Ph), 125.86 (Ph), 111.65 (CH_2=), 85.15 (Ts(OCb)*C*H), 51.47 (Ph(isopropenyl)*C*H), 45.54 (Cb), 45.07 (Cb), 20.52 (Ts), 20.07 (Cb), 19.93 (CH_3), 19.76 (Cb), 19.16 (Cb), 19.05 (Cb).

4.4.2. 2-Phenyl-1-tosyl-pent-4-enyl *N,N*-diisopropylcarbamate 7

From carbamate **11** (50 mg, 0.17 mmol), with a TMEDA/*s*-BuLi system, compound **7** (47 mg, 0.11 mmol, 61%) was obtained, whose GC and ^{1}H NMR match the reported data (from the diastereomeric mixture);[1] HRMS matches the calculated value; er on C1 (*R:S*): 88.8:11.2; er on C2 (*R:S*): 97.2:2.8; $[\alpha]_D^{20} = +39.6$ (*c* 1, $CHCl_3$). From carbamate **11** (50 mg, 0.17 mmol), with (−)-sparteine/*s*-BuLi system, compound **7** (29 mg, 0.066 mmol, 38%) was obtained, whose GC and ^{1}H NMR match the reported data (from the diastereomeric mixture);[1] HRMS matches the calculated value; er on C1 (*R:S*): 14.9:85.1; er on C2 (*R:S*): 96.3:3.7; $[\alpha]_D = +21.7$ (*c* 1, $CHCl_3$). The following interpretation of the analytical data of compound **6b**[1] can then be derived: $t_R = 24.09$ min (**7a** and *ent*-**7a**), 24.13 min (**7b** and *ent*-**7b**) (HP-5); Chiral HPLC: Eurocel 01 (5 μm, 250 × 4.6 mm, Knauer), *i*-PrOH/*n*-hexane: 1:150, 0.6 mL/min, 26 min (**7a**), 33 min (*ent*-**7a**); 40 min (**7b**), 45 min (*ent*-**7b**); NMR of (**7a** and *ent*-**7a**): ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm 7.53 (d, *J* = 8.3 Hz, 2H, Ts), 7.21–7.07 (m, 7H, Ts, Ph), 6.04 (d, *J* = 8.9 Hz, 1H, CH–O), 5.58–5.43 (m, 1H, CH=), 4.98–4.81 (m, 2H, CH_2=), 3.75–3.68 (m, 1H, Cb), 3.64–3.57 (m, 1H, CH-Ph), 3.07–3.02 (m, 1H, Cb), 2.85–2.79 (m, 1H, CH_2), 2.49–2.41 (m, 1H, CH_2), 2.31 (s, 3H, Ts), 0.84 (d, *J* = 6.8 Hz, 3H, Cb), 0.74 (d, *J* = 6.8 Hz, 3H, Cb), 0.69 (d, *J* = 6.8 Hz, 3H, Cb), 0.57 (d, *J* = 6.8 Hz, 3H, Cb); ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm 150.24 (C=O), 144.57 (Ts), 138.80 (Ph), 134.59 (CH=), 134.25 (Ts), 129.37 (2C, Ts), 129.10 (2C, Ts), 128.67 (Ph), 128.43 (Ph), 128.14 (Ph), 127.25 (Ph), 126.93 (Ph), 117.03 (CH_2=), 86.36 (CH–O), 46.58 (Cb), 46.01 (Cb), 44.40 (CH-Ph), 35.38 (CH_2), 21.55 (Ts), 20.15 (Cb), 20.00 (Cb), 19.85 (Cb), 19.71 (Cb); NMR of (**7b** and *ent*-**7b**): ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm 7.70 (d, *J* = 8.3 Hz, 2H, Ts), 7.21–7.07 (m, 7H, Ts and Ph), 6.00 (d, *J* = 6.2 Hz, 1H, CH–O), 5.58–5.43 (m, 1H, CH=), 4.98–4.81 (m, 2H, CH_2=), 4.18–4.11 (m, 1H, Cb), 3.49–3.42 (m, 1H, Cb), 3.64–3.57 (m, 1H, CH-Ph), 2.99–2.93 (m, 1H, CH_2), 2.59–2.51 (m, 1H, CH_2), 2.29 (s, 3H, Ts), 1.18 (d, *J* = 6.8 Hz, 3H, Cb), 1.14 (d, *J* = 6.8 Hz, 3H, Cb), 1.04 (d, *J* = 6.8 Hz, 3H, Cb), 0.90 (d, *J* = 6.8 Hz, 3H, Cb); ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm 151.25 (C=O), 144.84 (Ts), 138.89 (Ph), 135.10 (CH=), 134.68 (Ts-S), 129.53 (2C, Ts), 129.41 (2C, Ts), 128.94 (Ph), 128.43 (Ph), 128.14 (Ph), 127.25 (Ph), 126.93 (Ph), 117.60 (CH_2=), 87.97 (CH–O), 46.78 (Cb), 45.94 (Cb), 45.01 (CH-Ph), 37.06 (CH_2), 21.55 (Ts), 21.21 (Cb), 20.93 (Cb), 20.13 (Cb), 19.98 (Cb).

4.5. General procedures for the asymmetric ACA of compounds 5a,b to 6 and 7

(a) As described in Tables 2 and 3, the copper source (0.010 mmol, 5 equiv % of the sulfone) was stirred with an indicated ligand (0.012 mmol, 1.2 equiv of the copper source) at rt in the specified solvent (2 mL) for 30 min, and cooled to the indicated reaction temperature, followed by the addition of a sulfone **5a** or **5b** solution in toluene (100 mg/mL, 0.8 mL, 0.20 mmol). To this cooled mixture, the Grignard reagent (0.30 M in diethyl ether, 1.0 mL, 0.30 mmol, 1.5 equiv of the sulfone substrate) was added dropwise over a period of 5 h by a syringe pump. The reaction was then quenched at the reaction temperature with a solution of formic acid in MeOH (1.0 M, 0.3 mL, 0.3 mmol), and then treated with satd aq NH_4Cl and the internal standard (6.4 mg benzophenone and 6.4 mg di(*p*-tolyl) ether). The organic phase was then separated and the water phase was washed several times with diethyl ether. Each batch of the organic layers was filtered through a silica gel plug and the combined organic layers were evaporated to dryness. The residue containing **6** or **7** was analyzed by GC or chiral HPLC.[19]

(b) For reactions using NHC ligand **12** in Table 2, entry 1 and Table 3, entry 8, the triflate salt of ligand **12** (0.012 mmol, 4.6 mg) was mixed with 2 mL of diethyl ether, cooled to −30 °C, and treated with the corresponding Grignard reagent (0.30 M in diethyl ether, 0.05 mL, 0.015 mmol) used for the addition reaction. The mixture was stirred at −30 °C for 30 min, and to this, copper source (0.010 mmol, 5 equiv % of the sulfone) was then added. The resulting complex was again stirred at −30 °C for 30 min, and cooled to the indicated reaction temperature followed by the addition of a sulfone **5a** or **5b** solution in toluene (100 mg/mL, 0.8 mL, 0.20 mmol). To this cooled mixture, the Grignard reagent (0.30 M in diethyl ether, 1.0 mL, 0.30 mmol, 1.5 equiv of the sulfone substrate) was added dropwise over a period of 5 h by a syringe pump. The mixture was then quenched and analyzed in the same way as described in part (a).

(c) For a reversed addition as described in Table 3, entry 4, the reaction conditions are the same as described in part (a), except that the allylmagnesium bromide was added at a time to the cooled copper–ligand complex solution before the sulfone was added dropwise over a period of 5 h. The mixture was then quenched and analyzed in the same way as described in part (a).

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