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Copper-Catalysed Ring Opening of Polycyclic *meso*-Hydrazines with Trialkylaluminium Reagents and SimplePhos Ligands

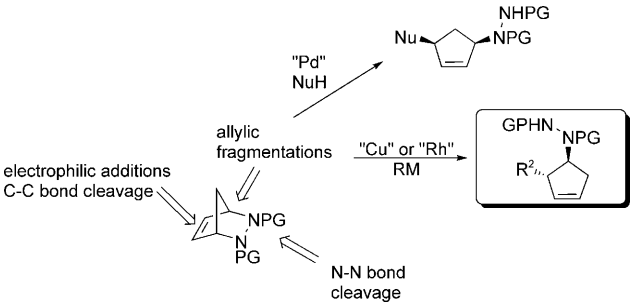
Laëtitia Palais,[a] Chloée Bournaud,[b] Laurent Micouin,[b] and Alexandre Alexakis*[a]

Abstract: *meso*-Hydrazines could be desymmetrised by ring-opening reactions by using various metal catalysts to form substituted cyclopentenes, which have a high synthetic potential. Herein, we report the asymmetric copper-catalysed ring opening of a range of polycyclic hydrazines with trialkylaluminium reagents and SimplePhos ligands with both high isolated yields and enantioselectivities of up to 95%.

Keywords: aluminum · copper · desymmetrization · hydrazines · P ligands

Introduction

The development of enantioselective reactions is still a challenge in synthetic chemistry. Desymmetrisation of *meso* compounds has attracted a lot of attention because one or more stereocentres can be easily generated by simple transformations.[1] For instance, *meso*-hydrazines, prepared from cyclopentadiene and diazo compounds, can be desymmetrised in different ways by using diastereoselective or enantioselective reactions.[2] Indeed, by starting from *meso*-hydrazines, chiral, substituted aminocyclopentenes can be easily prepared by functionalisation of the double bond (hydroboration,[3] hydroformylation,[4] dihydroxylation[5] and cyclopropanation[6]), followed by the cleavage of the N–N bond, and also by ring opening of the *meso* substrate by using metal catalysts (Pd,[7] Rh,[8] Cu;[9] Scheme 1). These products are useful intermediates for the synthesis of biologically active compounds.[2]



Scheme 1. Synthetic transformations of polycyclic *meso*-hydrazines.

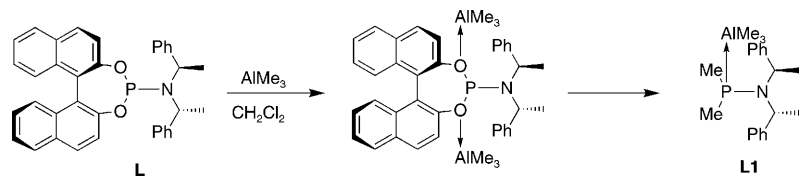
In this respect, we have described the copper-catalysed ring opening of polycyclic hydrazines by using phosphoramide BINOL-based ligands and aluminium reagents.[9b] We have demonstrated that the ligand was cleaved by trimethylaluminium in noncoordinating solvents, such as dichloromethane or toluene, to provide the corresponding phosphinamine, which is the real ligand in this catalytic reaction (Scheme 2).

Because the phosphinamine ligand has the same skeleton as our new family of SimplePhos ligands, we have used them in this type of reaction. Highly improved results were observed with SimplePhos ligands in comparison to dimethylphosphinamine ligand.[10] This novel class of ligand has already showed its efficiency in various asymmetric copper-catalysed reactions, such as conjugate addition to di- and trisubstituted enones,[10,11] allylic alkylation,[10] the kinetic resolution of vinyloxiranes[12] and also in desymmetrisation of *meso*-oxabenzonorbornadienes.[13]

We report herein a full account of our results in the copper-catalysed ring opening of bi- and tricyclic *meso*-hy-

[a] Dr. L. Palais, Prof. Dr. A. Alexakis
Département de chimie organique, Université de Genève
30 quai Ernest Ansermet
1211 Geneve 4 (Switzerland)
Fax: (+41) 223-793-215
E-mail: alexandre.alexakis@unige.ch

[b] Dr. C. Bournaud, Dr. L. Micouin
Laboratoire de Chimie Thérapeutique
UMR 8638, Faculté des Sciences Pharmaceutiques et Biologiques
4 avenue de l'Observatoire
75270 Paris Cedex 06 (France)
Fax: (+33) 143291403



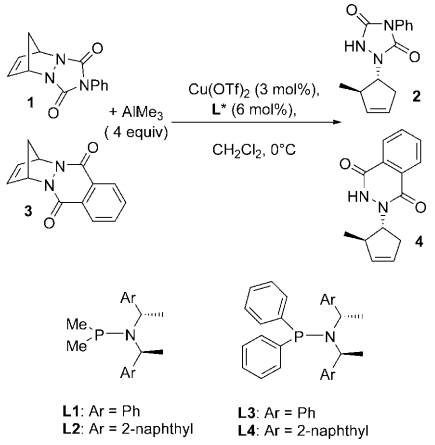
Scheme 2. Cleavage of phosphoramidite ligand by Me_3Al in noncoordinating solvents.

drazines with various trialkylaluminium reagents and SimplePhos ligands.

Results and Discussion

Previous results: In our preliminary report we compared the reactivity of our SimplePhos ligands with dimethylphosphinamine ligand **L1** in the asymmetric desymmetrisation of tricyclic hydrazines with Me_3Al and $Cu(OTf)_2$ as the copper salt (Table 1). We showed that SimplePhos ligands **L3** and **L4** gave better results in terms of reactivity and enantioselectivity, compared to the analogous ligands **L1** or **L2** (Table 1, entries 1 vs. 2 and 3 vs. 4), affording the corresponding disubstituted adducts with *ee*s of up to 94%.[10]

Table 1. Copper-catalysed ring-opening reaction of tricyclic hydrazines by Me_3Al with phosphinamine ligands (**L1**, **L2**) or SimplePhos ligands (**L3**, **L4**).

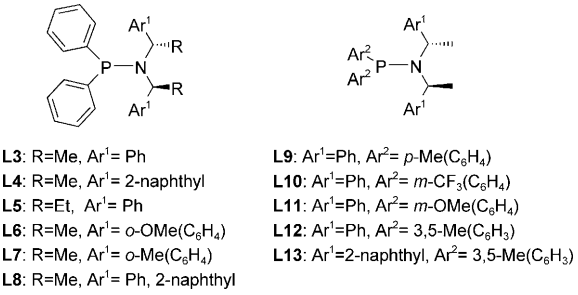


Entry	Substrate	Ligand	Yield [%]	*ee*[a] [%]
1	**1**	**L2**	85	85
2	**1**	**L4**	81	94
3	**3**	**L1**	94	79
4	**3**	**L3**	90	89

[a] Determined by using chiral SFC.

Tri- and bicyclic hydrazines: Because we had only tested a few ligands in the previous study, we envisaged this study as not only a screening of SimplePhos ligands, but also an opportunity to test other R_3Al aluminium reagents. All the ligands used in this study are summarised in Figure 1.

Firstly, we tested ligands that have amino groups with different electronic and steric effects (Table 2, entries 1–6). The two first entries show results that were obtained previously.[10]

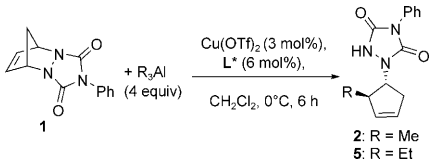


L3: R=Me, Ar^1= Ph
L4: R=Me, Ar^1= 2-naphthyl
L5: R=Et, Ar^1= Ph
L6: R=Me, Ar^1= *o*-OMe(C_6H_4)
L7: R=Me, Ar^1= *o*-Me(C_6H_4)
L8: R=Me, Ar^1= Ph, 2-naphthyl

L9: Ar^1=Ph, Ar^2= *p*-Me(C_6H_4)
L10: Ar^1=Ph, Ar^2= *m*-CF_3(C_6H_4)
L11: Ar^1=Ph, Ar^2= *m*-OMe(C_6H_4)
L12: Ar^1=Ph, Ar^2= 3,5-Me(C_6H_3)
L13: Ar^1=2-naphthyl, Ar^2= 3,5-Me(C_6H_3)

Figure 1. SimplePhos ligands that were used in this study.

Table 2. Copper-catalysed ring opening of tricyclic hydrazines **1** by using trialkylaluminium with various SimplePhos ligands.



Entry	R	Ligand	Yield [%]	*ee*[a] [%]
1	Me	**L3**	90	89
2	Me	**L4**	81	94
3	Me	**L5**	98	94
4	Me	**L6**	83	94
5	Me	**L7**	85	45
6	Me	**L8**	87	92
7	Me	**L9**	90	92
8	Me	**L10**	88	88
9	Me	**L11**	76	88
10	Me	**L12**	85	88
11	Me	**L13**	47	81
12	Et	**L3**	70	69
13	Et	**L4**	38	69
14	Et	**L5**	32	40
15	Et	**L6**	93	77
16	Et	**L9**	93	66
17	Et	**L10**	90	71
18	Et	**L11**	45	61
19	Et	**L12**	82	62

[a] Determined by using chiral SFC.

When the methyl group is replaced by a bulkier ethyl group (R in Figure 1) in ligand **L5**, the adduct is not only obtained in higher isolated yield (98%) but also in higher *ee* (94%; Table 2, entries 1 and 3). As we have observed before, an increase in the steric bulk of the amino part is favourable for high enantioselectivities. We also compared the reactivity of ligands with a substituent in the *ortho* position of the aryl group (**L6** and **L7**; Table 2, entries 4 and 5). The

presence of a methyl group in the *ortho* position has a dramatic effect on the enantioselectivity because an *ee* of only 45% was obtained. In contrast, a chelating group such as *o*-OMe gave a much better result, with an *ee* of up to 94%. Ligand **L8** with a non-C_2-symmetric amine gave an intermediate result of 92% *ee* and 87% yield (Table 2, entry 6).

Concerning the diaryl part on the phosphorous atom, all ligands with an electron-donating or withdrawing group in the *meta* position afforded the corresponding adduct with almost the same range of *ee*s (88%; Table 2, entries 8–10), except for ligand **L13** (with xylyl groups and a 2-naphthyl group on the amine unit), which showed a lower enantioselectivity of 47% (Table 2, entry 11). Finally, ligand **L9** with a methyl group in the *para* position on the diaryl part on the phosphorous atom catalysed the reaction with 92% yield and 92% *ee* (Table 2, entry 7).

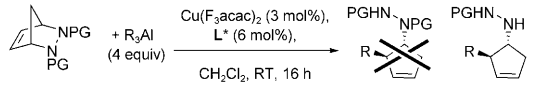
Then we investigated the addition of Et_3Al to this same hydrazine by using the same experimental conditions: 3 mol% of copper(II) triflate and 6 mol% of chiral ligands in dichloromethane at 0°C. Surprisingly, ligand **L5**, which gave the best result for the addition of Me_3Al gave lower conversion and enantioselectivity for the addition of Et_3Al (94% *ee* vs. 40%). Finally, the best ligand remained **L6** with only 77% *ee* and 93% isolated yield (Table 2, entry 15). All the other ligands showed a strong decrease in yield and *ee*.

The main problem with this type of tricyclic hydrazines is the difficulty of deprotecting the hydrazine part. Therefore, we decided to turn our attention to bicyclic hydrazines, which have a greater synthetic potential. Indeed, it should be easier to cleave the corresponding N–N bond to form the corresponding protected disubstituted amine.

For this study, we simply applied the same conditions that were used for tricyclic hydrazines with the $Cu(OTf)_2/CH_2Cl_2$ couple and the best ligand (**L6**) to bicyclic hydrazine **6**, which has benzyl carbamate (Cbz) as a protecting group. Because the bicyclic hydrazines are less reactive than the tricyclic one, the reaction was sluggish, and we not only needed to increase the temperature to room temperature but also the reaction time to 24 h instead of 6 h. Unfortunately, we were unable to isolate the corresponding adduct, the reaction was messy and several byproducts were observed. We therefore investigated other copper sources, and after a small screening, we found that copper trifluoroacety lacetonate ($[Cu(CF_3COCHCOCH_3)_2]$) was the best (Table 3).

Surprisingly, the obtained adduct was the deprotected one (on the first amine). Consequently, this product was less stable, and low isolated yields were observed despite good enantioselectivity of up to 87% (Table 3, entry 3). A small screening of ligands was tested with **L3**, **L4**, **L5**, **L9** and **L12**. Thus, the deprotected adduct could be obtained in 94% *ee*, at best, but again with a low isolated yield of 33% with ligand **L5**. To enlarge the scope of substrate, we briefly tested the addition of Me_3Al to the hydrazine with a *tert*-butyloxycarbonyl (Boc) protecting group, that is, compound **7**. Unfortunately, no reaction occurred at all. The same result was observed for the addition of Et_3Al to Cbz-hydrazine. In view of these results, we decided to reinvestigate the experimental conditions.

Table 3. Copper-catalysed ring opening of bicyclic hydrazines **6** and **7** by using trialkylaluminium with various SimplePhos ligands.



6: PG = Cbz
7: PG = Boc

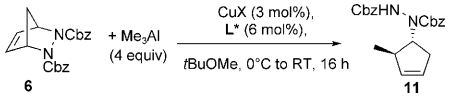
8: R = Me, PG = Cbz
9: R = Et, PG = Cbz
10: R = Me, PG = Boc

Entry	Substrate	R	Ligand	Yield[a] [%]	*ee*[c] [%]
1	**6**	Me	**L3**	(100)[b]	86
2	**6**	Me	**L4**	20	83
3	**6**	Me	**L5**	33	94
4	**6**	Me	**L6**	17	87
5	**6**	Me	**L9**	21	74
6	**6**	Me	**L12**	42	83
7	**7**	Me	**L5**	0	
8	**6**	Et	**L2**	0	

[a] Determined by ^1H NMR [b] Conversion %. [c] Determined by using chiral SFC.

Optimisation of experimental conditions: First, we screened several solvents. Neither performing the reaction in toluene nor in methyl-THF gave the corresponding product. In diethyl ether, the hydrazine was not soluble at all. The last test, in *tert*-butylmethyl ether (MTBE) and with $[Cu(CF_3COCHCOCH_3)_2]$ as the copper salt, afforded the desired product with full conversion and 76% *ee* (Table 4, entry 1). No deprotection of the hydrazine occurred. Thus with MTBE as the solvent, we screened several copper salts and various ligands (Table 4). No improvement of the enantioselectivity was observed with copper(II) triflate or acetate (Table 4, entries 2 and 3). On the other hand, a small increase in *ee* was observed with CuTC (77%), (CuTC = copper thiophene carboxylate) and the corresponding adduct was obtained in 86% isolated yield, which is a clear improvement over the previous conditions (Table 4, entry 4).

Table 4. Optimisations of experimental conditions: Copper salts and solvents.



6 **11**

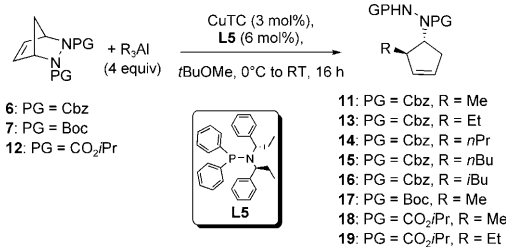
Entry	Ligand	CuX	Conv.[a] [%]	*ee*[b] [%]
1	**L3**	$[Cu(CF_3COCHCOCH_3)_2]$	100	76
2	**L3**	$Cu(OTf)_2$	100	74
3	**L3**	$Cu(OAc)_2{\cdot}H_2O$	100	75
4	**L3**	CuTC	100 (86)	77
5	**L4**	CuTC	100	78
6	**L5**	CuTC	100 (89)	87
7	**L6**	CuTC	100	86
8	**L8**	CuTC	100	75
9	**L12**	CuTC	100	69

[a] Determined by ^1H NMR spectroscopy; the value in parentheses in is the isolated yield. [b] Determined by using chiral SFC.

Decreasing the temperature to 0 °C did not improve the enantioselectivity, and at lower temperature (−30 °C), no reaction occurred. Concerning the ligands, **L4** with a 2-naphthyl group on the amine part did not improve the result observed with the simplest ligand, **L3** (Table 4, entry 5). This same observation was made with ligands **L8** and **L12** with a xylyl group on the aryl part on the phosphorous atom (Table 4, entries 8–9). Moreover, ligands **L5** and **L6** showed better enantioselectivities with almost the same *ee* (Table 4, entries 6–7), with a slight increase in favour of ligand **L5** (87 % *ee*). With ligand **L5**, the corresponding disubstituted cyclopentene was obtained in 89 % isolated yield.

With these optimised conditions in hand, we decided to use 3 mol % of CuTC and 6 mol % of **L5** in MTBE to screen all commercially available trialkylaluminium (R_3Al) compounds with a range of hydrazines with different protecting groups **6**, **7** and **12**, to see if the new system is viable (Table 5).

Table 5. Copper-catalysed ring opening of bicyclic hydrazines by trialkylaluminium with SimplePhos ligand **L5** under new conditions.



Entry	Substrate	R	Yield [%]	*ee*[a] [%]
1	**6**	Me	89	87
2	**6**	Et	84	76
3	**6**	*n*Pr	71	64
4	**6**	*n*Bu	85	60
5	**6**	*i*Bu	90	77
6	**7**	Me	90 (81)[b]	94 (95)[b]
7	**12**	Me	89	84
8	**12**	Et	80	83

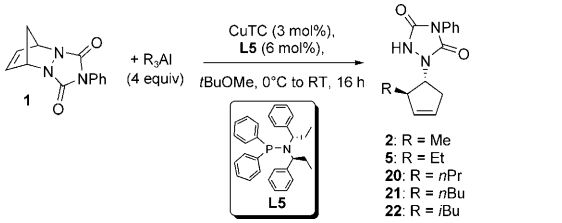
[a] Determined by using chiral SFC or chiral GC. [b] The value in parentheses is the yield/*ee* when the reaction was carried out on a 1 mmol scale.

Firstly, the previously examined bicyclic hydrazine with a Cbz group, compound **6**, was screened (Table 5, entries 1–5). Although Me_3Al gave 87 % *ee*, we observed that the enantiomeric excesses decreased with the length of the alkyl chain, from 87 % with a methyl group to 60 % with a *n*-butyl chain. Interestingly, the addition of an isobutyl group afforded the desired adduct with a higher *ee* of up to 77 %. Whatever the length of the alkyl chain, all the isolated yields were high.

Then, to check the influence of the protecting group, we performed the reaction with bicyclic hydrazines that had a Boc group (compound **7**) or a CO_2iPr group (compound **12**) as the protecting group (Table 5, entries 6–8). The addition of Me_3Al provided the cyclopentene adduct with 90 % isolated yield and 94 % *ee* with the Boc-hydrazine, whereas *ee*s of only 84 and 87 % were observed with hydrazine **12** and Cbz-hydrazine **6**, respectively (Table 5, entries 6 vs. 1 and 6 vs. 7). A more sterically demanding protecting group seems to increase the enantioselectivity. Moreover, the same reaction on a 1 mmol scale afforded the adduct with almost the same isolated yield of 81 % and a higher *ee* (95 %). The addition of Et_3Al to hydrazine **12** (Table 5, entry 8) worked well, giving 80 % isolated yield and almost the same *ee* as that observed with the addition of a methyl group (83 %).

The addition of Me_3Al to tricyclic hydrazine **1** under these new experimental conditions afforded desired adduct **2** with exactly the same *ee* as the old conditions (Table 2, entry 3 vs. Table 6, entry 1). In contrast, the addition of

Table 6. Copper-catalysed ring opening of tricyclic hydrazine **1** by trialkylaluminium with SimplePhos ligand **L5** under new conditions.



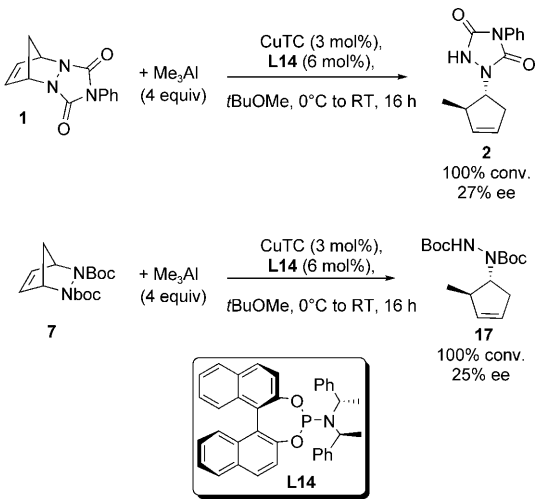
Entry	R	Yield [%]	*ee*[a] [%]
1	Me	80	94
2	Et	90	90
3	*n*Pr	72	86
4	*n*Bu	97	83
5	*i*Bu	40	71

[a] Determined by using chiral SFC.

Et_3Al showed higher enantioselectivity with **L5** (90 % instead of 40 %), but was better than the previous best ligand **L6** (77 % *ee*; Table 2 entries 13–14 vs. Table 6 entry 2). A small decrease in the yield and the *ee* was observed with the addition of an *n*-propyl and *n*-butyl chain (Table 6, entries 3, 4), similar to that observed with bicyclic hydrazine **6** (see Table 6). Finally, the addition of an isobutyl group was tested, but a low isolated yield of 40 % and a moderate *ee* (71 %) were obtained (Table 6, entry 5).

Finally, we needed to check the behaviour of phosphoramidite-type ligands in these new experimental conditions, that is, trialkylaluminium in MTBE. Consequently, we decided to investigate the possible reaction of BINOL-phosphoramidite ligand **L14** with Me_3Al in MTBE by using NMR spectroscopy. To our surprise, after 10 h at room temperature we observed a cleavage of the ligand, as was also the case in noncoordinating solvents (^{31}P NMR: $\delta = 145$ ppm for **L14** and 27 ppm for **L1**). This observation was confirmed by the experimental reaction (Scheme 3).

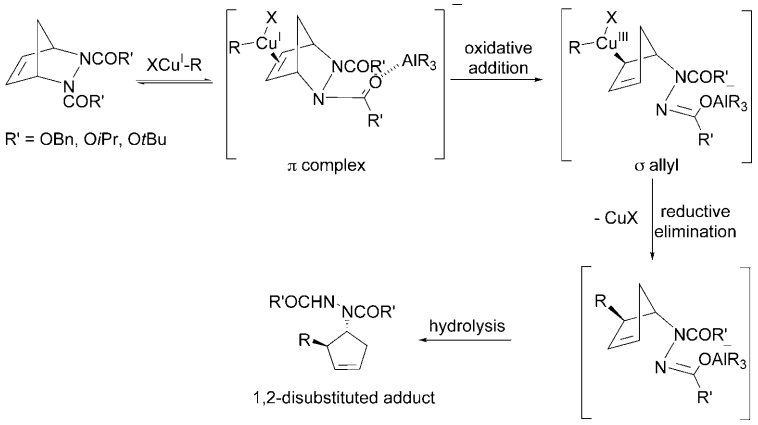
Ligand **L14** was cleaved to give the corresponding dimethylphosphinamine ligand **L1**, which clearly showed poorer results in terms of enantioselectivity (27 % *ee* for adduct **2** and 25 % *ee* for **17**) than SimplePhos ligands.



Scheme 3. Ring opening of *meso*-hydrazines **1** and **7** by Me_3Al in presence of **L14**.

Mechanistic aspects: In the rhodium-catalysed ring-opening reaction of *meso*-hydrazines, the mechanistic pathway has been shown to be an enantioselective carbometalation followed by a β-elimination reaction.[2,8,14] A similar pathway has also been disclosed for the palladium-catalysed ring opening.[2,15] However, in some cases the enantioselective desymmetrisation occurs by selective Pd insertion into the C–N bond and formation of a π-allyl intermediate.[7a] In these cases, the stereochemical and regiochemical outcome is different, with formation of the *cis*-1,3-disubstituted cyclopentene adduct.

In the present copper-catalysed reactions, we believe that the mechanistic pathway follows a classical S_N' allylic substitution.[16] Thanks to the assistance of the Lewis acidic R_3Al reagent, the NCO functionality is sufficiently activated to act as a leaving group. The formation of the π-copper(I) complex leads to the subsequent stereochemistry-determining step, namely, the oxidative addition of the copper, *anti* with respect to the leaving group, into σ-allyl Cu^{III} species.[17] Finally, after reductive elimination and hydrolysis, the *trans*-1,2-disubstituted adduct is obtained (see Scheme 4).



Scheme 4. Mechanistic pathway.

Conclusions

In summary, we have reported the desymmetrisation of polycyclic hydrazines with high enantiomeric excesses (up to 95%) by using various trialkylaluminium reagents and copper salts with SimplePhos ligand **L5**. In contrast to similar Pd and Rh-catalysed reactions, in which only sp^2-type carbon nucleophiles are allowed, the present method allows alkyl groups to be transferred. The solvent plays a crucial role in the success of this reaction, and MTBE was the best. Finally, in contrast to phosphoramidite-type ligands, SimplePhos ligands were very stable in presence of trialkylaluminium in both non-coordinating solvents and ethereal solvents, such as MTBE; no cleavage was observed.

Experimental Section

General procedure for the copper-catalysed ring opening of polycyclic hydrazines with organoaluminium and SimplePhos ligand L5: CuTC (3 mol%) and the ligand (6 mol%) in dry MTBE (1 mL) were placed in a flame-dried Schlenk tube, and the mixture was stirred at RT for 20 min. A solution of bicyclic hydrazine (0.25 mmol) in dry MTBE (0.5 mL) was added to the mixture, and the solution was cooled to 0°C. Trialkylaluminium (1 mmol) was added, then the reaction was stirred at RT overnight. The reaction was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The crude was purified by flash chromatography (elution conditions: cyclohexane/EtOAc 8:2 or 6:4) to afford the desired compound. ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker 400 FTNMR in $CDCl_3$ unless otherwise stated, and chemical shift (δ) are given in ppm relative to residual $CHCl_3$. Multiplicity is indicated as follows: s (singulet), d (doublet), t (triplet), quint (quintuplet), m (multiplet), brs (broad singlet). Coupling constants are reported in Hertz (Hz).

Dibenzyl 1-[(1*S*,2*S*)-2-methylcyclopent-3-enyl]hydrazine-1,2-dicarboxylate (11): Enantiomeric excess was measured by chiral SFC (CHIRACEL AD, 10% MeOH flow rate: 2 mL min^{-1}), $R_{t_1}=6.97$, $R_{t_2}=7.43$; $[\alpha]_D^{20}=-35.8$ ($c=1.00$ in $CHCl_3$, 87% *ee*); ^1H NMR (500 MHz, $CDCl_3$, 50°C): $\delta=7.32$ (m, 10H), 6.51 (brs, 1H), 5.56 (m, 2H), 5.15 (d, $J=7$ Hz, 4H), 4.48 (m, 1H), 2.81 (m, 1H), 2.54–2.45 (m, 2H), 1.1 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 50°C): $\delta=206.5$, 156.7, 156.1, 1362, 135.8, 135.3, 128.66, 128.63, 128.45, 128.28, 128.25, 128, 68.2, 67.9, 66.1, 42.7, 35.2, 30.8, 18.7 ppm; IR (neat): $\tilde{\nu}=3286$ (w), 2957 (w), 1712 (s), 1219 (s), 740 (m), 696 cm^{-1} (s); HRMS (ESI): *m*/*z* calcd for $C_{22}H_{24}N_2O_4+Na$: 403.1628; found: 403.1637.

Dibenzyl 1-[(1*S*,2*S*)-2-ethylcyclopent-3-enyl]hydrazine-1,2-dicarboxylate (13): Enantiomeric excess was measured by chiral SFC (CHIRACEL AD, 10% MeOH flow rate: 2 mL min^{-1}), $R_{t_1}=6.64$, $R_{t_2}=7.41$; $[\alpha]_D^{20}=-35.9$ ($c=1.00$ in $CHCl_3$, 76% *ee*); ^1H NMR (500 MHz, $CDCl_3$, 50°C): $\delta=7.31$ (m, 10H), 6.51 (brs, 1H), 5.62 (m, 2H), 5.14 (d, $J=8.8$ Hz), 4.59 (m, 1H), 2.69–2.45 (m, 3H), 1.54 (m, 1H), 1.38 (m, 1H), 0.91 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 50°C): $\delta=156.6$, 155.9, 136.2, 135.9, 133.2, 128.64, 128.61, 128.4, 128.27, 128.23, 128, 68.2, 67.9, 63.5, 49.8, 35.5, 26.4, 11.6 ppm; IR (neat): $\tilde{\nu}=3285$ (w), 2959 (w), 2925 (w), 1711 (s), 1216 (s), 741 (m), 696 cm^{-1} (s); HRMS (ESI): *m*/*z* calcd for $C_{23}H_{26}N_2O_4$: 395.1965; found: 395.1963$^+$.

Dibenzyl 1-[(1*S*,2*S*)-2-propylcyclopent-3-enyl]hydrazine-1,2-dicarboxylate (14): Enantiomeric excess was measured by chiral SFC (CHIRACEL AS, 10% MeOH flow rate: 2 mL min^{-1}), R_{t_1} = 3.73, R_{t_2} = 4.25; $[\alpha]_D^{20}$ = −41.4 (c = 1.00 in $CHCl_3$, 64% *ee*); ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C): δ = 7.32 (m, 10H), 6.44 (brs, 1H), 5.61 (m, 2H), 5.15 (m, 4H), 4.57 (m, 1H), 2.73–2.43 (m, 3H), 1.47 (m, 1H), 1.33 (m, 3H), 0.87 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): δ = 156.7, 155.9, 136.2, 135.9, 133.5, 128.66, 128.63, 128.4, 128.3, 128.2, 128, 68.2, 67.9, 64, 48.3, 36.1, 35.4, 20.7, 14.3 ppm; IR (neat): $\tilde{\nu}$ = 3286 (w), 2957 (w), 2928 (w), 1742 (s), 1674 (s), 1425 (s), 1211 (s), 728 cm^{-1} (s), 696 (s); HRMS (ESI): m/z calcd for $C_{24}H_{28}N_2O$: 409.2121; found: 409.2135.

Dibenzyl 1-[(1*S*,2*S*)-2-butylcyclopent-3-enyl]hydrazine-1,2-dicarboxylate (15): Enantiomeric excess was measured by chiral SFC (CHIRACEL AD, 10% MeOH flow rate: 2 mL min^{-1}), R_{t_1} = 6.25, R_{t_2} = 7.02; $[\alpha]_D^{20}$ = −37.7 (c = 1.00 in $CHCl_3$, 60% *ee*); ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C): δ = 7.31 (m, 10H), 6.47 (brs, 1H), 5.61 (m, 2H), 5.15 (m, 4H), 4.57 (m, 1H), 2.72–2.41 (m, 3H), 1.49 (m, 1H), 1.27 (m, 5H), 0.87 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): δ = 156.7, 156, 136.2, 135.9, 133.5, 128.65, 128.63, 128.4, 128.28, 128.23, 128, 68.2, 67.9, 63.9, 48.4, 35.4, 33.5, 29.7, 23, 14.0 ppm; IR (neat): $\tilde{\nu}$ = 3287 8w), 2955 (w), 2926 (m), 2856 (w), 1713 (s), 1410 (s), 1216 (s), 741 (m), 696 cm^{-1} (s); HRMS (ESI): m/z calcd for $C_{25}H_{30}N_2O_4$: 423.2278; found: 423.2296.

Dibenzyl 1-[(1*S*,2*S*)-2-isobutylcyclopent-3-enyl]hydrazine-1,2-dicarboxylate (16): Enantiomeric excess was measured by chiral SFC (CHIRACEL AD, 10% MeOH flow rate: 2 mL min^{-1}), R_{t_1} = 5.46, R_{t_2} = 6.65; $[\alpha]_D^{20}$ = −38.9 (c = 1.00 in $CHCl_3$, 60% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (m, 10H), 6.49 (brs, 1H), 5.62 (m, 2H), 5.62 (m, 4H), 4.54 (m, 1H), 2.77–2.43 (m, 3H), 1.68 (m, 1H), 1.26 (m, 2H), 0.87 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.5, 136.0, 135.7, 133.5, 128.66, 128.61, 128.4, 128.2, 128, 67.8, 46.3, 43.4, 35.2, 29.8, 26.4, 23.4, 22.3 ppm; IR (neat): $\tilde{\nu}$ = 3279 (w), 2954 (w), 1742 (s), 1676 (s), 1423 (m), 1211 (s), 728 (m), 696 cm^{-1} (s); HRMS (ESI): m/z calcd for $C_{25}H_{30}N_2O_4$: 423.2278; found: 423.2281.

Di-*tert*-butyl-1-[(1*S*,2*S*)-2-methylcyclopent-3-enyl]hydrazine-1,2-dicarboxylate (17): Enantiomeric excess was measured by chiral GC (CHIRASIL-DEX-CB, isotherm T = 150 °C), R_{t_1} = 25.91, R_{t_2} = 26.91; $[\alpha]_D^{20}$ = −57.6 (c = 1.01 in $CHCl_3$, 60% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.25 (brs, 1H), 5.54–5.52 (m, 2H), 4.40 (m, 1H), 2.71 (m, 1H), 2.43–2.39 (m, 2H), 1.42 (s, 18H), 1.07 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.4, 135.5, 128.1, 127.9, 81.0, 77.4, 64.8, 42.6, 35.1, 28.4, 18.9 ppm; IR (neat): $\tilde{\nu}$ = 3322 (w), 2977 (m), 1705 (s), 1393 (s), 1366 (s), 1158 cm^{-1} (s); HRMS (ESI): m/z calcd for $C_{16}H_{28}N_2O_4$: 313.2121; found: 313.2111.

Diisopropyl 1-[(1*S*,2*S*)-2-methylcyclopent-3-enyl]hydrazine-1,2-dicarboxylate (18): Enantiomeric excess was measured by chiral GC (CHIRASIL-DEX-CB, isotherm T = 150 °C), R_{t_1} = 24.23, R_{t_2} = 25.81; $[\alpha]_D^{20}$ = −82.6 (c = 0.77 in $CHCl_3$, 60% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.36 (brs, 1H), 5.57–5.51 (m, 2H), 4.94–4.91 (m, 2H), 4.44 (m, 1H), 2.76 (m, 1H), 2.47–2.42 (m, 2H), 1.23 (d, J = 2.7 Hz, 12H), 1.09 ppm (d, J = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.4, 155.8, 135.5, 125.4, 135.3, 128.1, 127.8, 127.6, 70.0, 69.7, 65.5, 42.5, 35.0, 22.1, 22.0, 18.6 ppm; IR (neat): $\tilde{\nu}$ = 3298 (w), 2980 (w), 1708 (s), 1687 (s), 1374 8 m), 1108 (s), 762 (m); HRMS (ESI): m/z calcd for $C_{14}H_{24}N_2O_4$: 285.1808; found: 285.1815.

Diisopropyl 1-[(1*S*,2*S*)-2-ethylcyclopent-3-enyl]hydrazine-1,2-dicarboxylate (19): Enantiomeric excess was measured by chiral GC (HYDRODEX-B-3P, isotherm T = 140 °C), R_{t_1} = 62.32, R_{t_2} = 63.94; $[\alpha]_D^{20}$ = 39.3 (c = 0.75 in $CHCl_3$, 60% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.22 (brs, 1H), 5.63 (m, 2H), 4.94 (m, 2H), 4.55 (m, 1H), 2.66–2.43 (m, 3H), 1.67–1.57 (m, 2H), 1.25 (d, J = 5.8 Hz, 12H), 0.93 ppm (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 129.4, 128.3, 128.0, 70.1, 69.8, 49.7, 35.3, 29.8, 26.3, 22.23, 22.20, 22.0, 12.3, 11.7 ppm; IR (neat): $\tilde{\nu}$ = 3299 (w), 2980 (w), 1702 (s), 1373 (m), 1105 (s), 761 cm^{-1} (m); HRMS (ESI): m/z calcd for $C_{15}H_{26}N_2O_4$: 299.1965; found: 299.1962.

4-Phenyl-1-[(1*S*,2*S*)-2-methylcyclopent-3-enyl]-1,2,4-triazolidine-3,5-dione (2): Enantiomeric excess was measured by chiral SFC (CHIRACEL AD, 10% MeOH flow rate: 2 mL min^{-1}), R_{t_1} = 7.61, R_{t_2} = 11.68; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44–8.46 (m, 1H), 8.09–8.11 (m, 1H), 7.79–7.82 (m, 2H), 5.50–5.56 (m, 2H), 5.43 (dt, J = 9.0 Hz, J = 7.0 Hz, 1H), 2.92–2.95 (m, 1H), 2.64–2.67 (m, 1H), 2.47–2.54 (m, 1H), 1.07 ppm (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 158.8, 151, 135.2, 133.0, 132.6, 129.4, 127.6, 127.5, 124.8, 124.6, 62.9, 44.8, 37.0, 19.1 ppm.

4-Phenyl-1-[(1*S*,2*S*)-2-ethylcyclopent-3-enyl]-1,2,4-triazolidine-3,5-dione (5): Enantiomeric excess was measured by chiral SFC (CHIRACEL OB, 5% MeOH flow rate: 2 mL min^{-1}), R_{t_1} = 4.5, R_{t_2} = 5.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42–8.48 (m, 1H), 8.09–8.13 (m, 1H), 7.79–7.86 (m, 2H), 5.51–5.69 (m, 3H), 2.74–2.90 (m, 2H), 2.55 (dd, J = 16.0 Hz, J = 6.0, 1H), 1.41–1.56 (m), 0.9 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 157.9, 152.0, 133.4, 132.9, 132.6, 129.4, 128.3, 127.7, 124.8, 60.0, 52.1, 37.3, 27.0, 11.7 ppm.

4-Phenyl-1-[(1*S*,2*S*)-2-propylcyclopent-3-enyl]-1,2,4-triazolidine-3,5-dione (20): Enantiomeric excess was measured by chiral SFC (CHIRACEL OJ, 10% MeOH flow rate: 2 mL min^{-1}), R_{t_1} = 3.45, R_{t_2} = 4.69; $[\alpha]_D^{20}$ = −66.9 (c = 1.00 in $CHCl_3$, 72% *ee*); ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C): δ = 7.54–7.52 (m, 2H), 7.46 (t, 2H, J = 7.8 Hz), 7.36 (t, J = 7.29, 1H), 5.73 (m, 2H), 4.60 (quint, J = 4.4 Hz, 1H), 2.81–2.75 (m, 2H), 2.48–2.43 (m, 1H), 1.50–1.38 (m, 4H), 0.93 ppm (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): δ = 153.6, 152.3, 133.8, 131.7, 129.2, 128.2, 128.1, 125.6, 60.8, 49.4, 36.2, 35.7, 20.7, 14.2 ppm; IR (neat): $\tilde{\nu}$ = 3061 (w), 2956 (w), 1686 (s), 1420 (m), 711 cm^{-1} (m); HRMS (ESI): m/z calcd for $C_{16}H_{19}N_3O_2$: 286.1550; found: 286.1540.

4-Phenyl-1-[(1*S*,2*S*)-2-butylcyclopent-3-enyl]-1,2,4-triazolidine-3,5-dione (21): Enantiomeric excess was measured by chiral SFC (CHIRACEL IC, 10% MeOH flow rate: 2 mL min^{-1}), R_{t_1} = 5.81, R_{t_2} = 7.26; $[\alpha]_D^{20}$ = −73.5 (c = 1.00 in $CHCl_3$, 83% *ee*); ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C): δ = 8.1 (m, 1H), 7.52 (m, 2H), 7.46 (t, J = 6.6 Hz, 2H), 7.36 (t, J = 7.6 Hz, 2H), 5.70 (m, 2H), 4.58 (quint, J = 4.7 Hz, 1H), 2.79–2.73 (m, 2H), 2.47–2.43 (m, 1H), 1.49–1.37 (m, 5H), 0.92 ppm (t, J = 6.9 Hz, 3H,); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): δ = 153.8, 152.2, 133.7, 131.7, 129.1, 128.2, 128, 125.6, 60.8, 49.3, 36.2, 35.6, 20.6, 14.2 ppm; IR (neat): $\tilde{\nu}$ = 3060 (w), 2956 (w), 1686 (s), 1421 (m), 713 cm^{-1} (m); HRMS (ESI): m/z calcd for $C_{17}H_{21}N_3O_2$: 300.1706; found: 300.1702.

4-Phenyl-1-[(1*S*,2*S*)-2-isobutylcyclopent-3-enyl]-1,2,4-triazolidine-3,5-dione (22): Enantiomeric excess was measured by chiral SFC (CHIRACEL OJ, 10% MeOH flow rate: 2 mL min^{-1}), R_{t_1} = 2.79, R_{t_2} = 3.77. $[\alpha]_D^{20}$ = −38.7 (c = 0.98 in $CHCl_3$, 71% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.35 (m, 5H), 5.70–5.66 (m, 2H), 4.55 (quint, 4.8 Hz, 1H), 2.84 (brs, 1H), 2.77–2.71 (m, 1H), 2.51–2.41 (m, 1H), 1.70 (sept, J = 6.8 Hz, 1H), 1.37–1.23 (m, 2H), 0.87 ppm (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.8, 151.9, 133.6, 131.4, 129.1, 128.2, 127.8, 125.5, 60.9, 53.5, 47.1, 43.4, 35.4, 26.2, 23.0, 22.5 ppm; IR (neat): $\tilde{\nu}$ = 3061 (w), 2955 (w), 1687 (s), 1420 (m), 710 cm^{-1} (m); HRMS (ESI): m/z calcd for $C_{17}H_{21}N_3O_2$: 300.1706; found: 300.1732.

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