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Sequential Copper-Catalyzed Rearrangement–Allylic Substitution of Bicyclic Hydrazines with Grignard Reagents

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Abstract: The problem of the synthesis of *trans*-1,4-disubstituted hydrazino- and aminocyclopentenes has been resolved by a sequential copper-catalyzed rearrangement–allylic alkylation of 2,3-diazabicyclo-[2.2.1]heptenes. The *cis*-fused 5,5-membered allylic carbazate which is formed *in situ* by a novel copper(II) triflate [$Cu(OTf)_2$]/(±)-BINAP-catalyzed rearrangement, can be alkylated with a broad spectrum of Grignard reagents with a predominant S_N2'-regioselectivity. The N-Boc protecting group proved to be optimal as regards yields, reaction times and regioselectivities.

Keywords: allylic alkylation; copper; Grignard reagents; rearrangement; sequential reactions

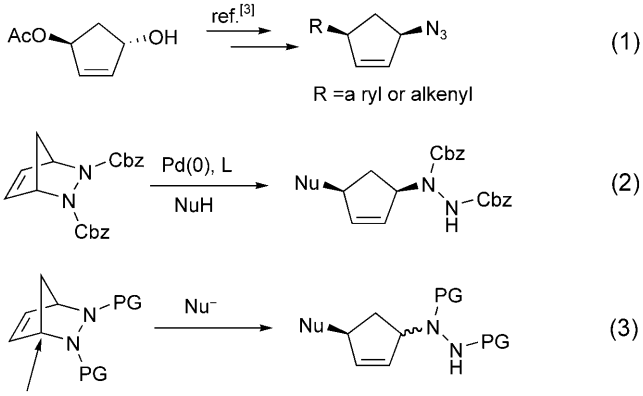


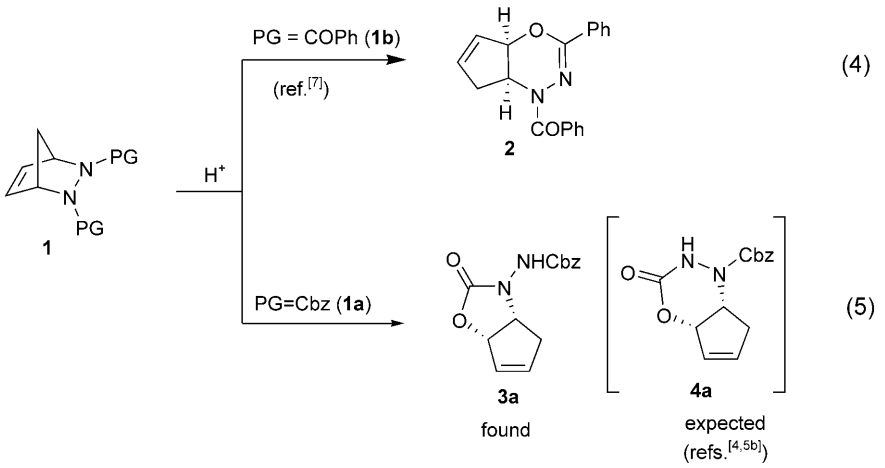
Figure 1. Possible approach to 1,4-substituted azido- or hydrazinocyclopentenes.

Substituted aminocyclopentenes hold a tremendous amount of synthetic potential as intermediates for the preparation of a variety of biologically interesting molecules.[1] For example, 4-amino-2-cyclopentene-1-methanol is a widely used chiral building block for the preparation of carbocyclic adenosine derivatives which possess antiviral properties.[2] Installation of a carbon-based nucleophile onto a pre-existing cyclopentene represents a viable strategy to introduce substitution on this ring. For example, the allylic displacement of 4-cyclopentene-1,3-diol monoacetate with aryl- and alkenyl-Grignard reagents followed by substitution of the hydroxy group with $(PhO)_2P(=O)N_3$ gave *cis*-1,4-azidoarylcyclopentenes [Eq. (1), Figure 1].[3a] *cis*-1,4-Disubstituted bis-Cbz-protected hydrazinocyclopentenes can be obtained by a diastereoselective palladium-catalyzed ring opening of Cbz-protected bicyclic hydrazine (**1a**) with soft nucleophiles [Eq. (2), Figure 1).[4] Quite recently, several methods for the ring opening of bicyclic hydrazines with carbon nucleophiles were developed, but all reported methods gave invariably 1,2-disubstituted hydrazinocyclopentenes.[5] It should be noted that Grignard reagents, which are the most readily available organometallic reagents, were never considered.

Furthermore, it is known that the direct nucleophilic displacement at the bridgehead position of [2.2.1]bicyclic systems, which can be a reasonable pathway to these compounds, is reported to be extremely difficult [Eq. (3), Figure 1].[6]

We report here a novel regioselective synthesis of *trans*-1,4-disubstituted hydrazino- and aminocyclopentenes by a sequential copper-catalyzed rearrangement–allylic alkylation of 2,3-diazabicyclo-[2.2.1]heptenes.

The thermal or Lewis acid-catalyzed rearrangement of bicyclic [2.2.1] diacylhydrazines, such as **1b**, to give oxadiazines has been extensively studied and explained on the basis of a [3,3]-sigmatropic (hetero-Cope) rearrangement [Eq. (4), Scheme 1].[7] More recently, the corresponding protic or Lewis acid-catalyzed (LA) rearrangement of carbobenzyloxy-protected bicyclic [2.2.1] hydrazine **1a** was explained by means of a transient allylic cation to give 5,6-bicyclic



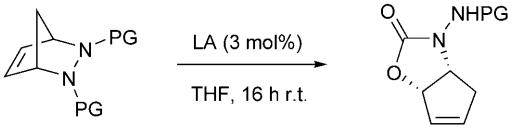
Scheme 1. Modes of rearrangement of differently protected [2.2.1] bicyclic hydrazines.

intermediate **4a** [Eq. (5), Scheme 1].[4,5b] As compound **4a** has an allylic leaving group, we considered this compound as a possible candidate for an allylic alkylation with Grignard reagents. However, in our hands, when bicyclic hydrazine **1a** was allowed to react with H_2SO_4 in CF_3CH_2OH in accordance with a previously reported procedure,[5b] a remarkably different reaction outcome was obtained. To our surprise, the main product was not the expected 5,6-bicyclic carbazate **4a** but the 5,5-analogue **3a** (65% isolated yield).[8]

In order to improve the yields of allylic carbazate of type **3**, the rearrangement of differently carbamoyl protected bicyclic hydrazines **1a**, **1c**, **1d** was investigated under the catalysis of different Lewis acids (Table 1). Using catalytic amounts (3.0 mol%) of $Cu(OTf)_2$ we soon realized that the *N-tert*-butoxycarbonyl (Boc) protected hydrazine **1c** was much more prone to the rearrangement reaction than **1a** (entry 1), and **1d** (entry 2), and afforded cleanly the corresponding carbazate **3c** as a white solid (entry 3). Copper(I) and copper(II) salts with a coordinating ligand (entries 4–6), proved to be ineffective for this rearrangement. On the other hand, also $Sc(OTf)_3$ and $FeCl_3$ promoted this kind of transformation in high yields (entries 7 and 8), whereas $Zn(OTf)_2$ gave a very low conversion (entry 9). The effect of adding phosphorus-based ligands to the reaction catalyzed by $Cu(OTf)_2$ was also examined. Very interestingly we found that the reaction performed in the presence of (±)-BINAP (6 mol%) was particularly efficient and complete conversion was observed in 10 min at room temperature (entry 10).[9] A similar result can be obtained by the use of non-coordinating solvents such as CH_2Cl_2 or toluene (data not shown in Table 1).

The detection by MS of dimeric structures,[5b] and the polymerization of THF suggested a stepwise mechanism with the involvement of open cationic species at least for N-Cbz protected compound **1a**.[8b] However, for the copper-catalyzed reaction of the N-Boc derivative **1c**, the rather small solvent effect together with the failure of detection of cationic intermediates, point to a concerted cyclic mechanism which can formally be interpreted as a [3,4]-sigmatropic rearrangement. In this scenario, the azaphilic

Table 1. Screening of Lewis acids (LA) for the rearrangement of [2.2.1] bicyclic hydrazines.[a]



1a, PG = Cbz
1c, PG = Boc
1d, PG = COOEt

3a, PG = Cbz
3c, PG = Boc

Entry	Substrate	Lewis Acid	Conversion [%]	Yield [%][b]
1[c]	**1a**	$Cu(OTf)_2$	95	58 (**3a**)
2[c]	**1d**	$Cu(OTf)_2$	complex mixture	
3	**1c**	$Cu(OTf)_2$	100	97 (**3c**)
4	**1c**	CuCl	< 5	N.d.
5	**1c**	$Cu(CH_3CN)BF_4$	< 10	N.d.
6	**1c**	$CuCl_2$	< 10	N.d.
7	**1c**	$Sc(OTf)_3$	100	82 (**3c**)
8[d]	**1c**	$FeCl_3$	95	80 (**3c**)
9	**1c**	$Zn(OTf)_2$	< 10	N.d.
10[e]	**1c**	$Cu(OTf)_2$	100	97 (**3c**)

[a] *Conditions:* **1a** or **1c**, Lewis acid (3 mol%) in THF at room temperature for 16 h, unless stated otherwise.
[b] Isolated yields after chromatographic purification on silica gel.
[c] The reaction has been carried out in CH_2Cl_2 because in THF extensive polymerization of the solvent was observed.
[d] 8 mol% of this salt was used.
[e] The reaction was carried out in the presence of 6 mol% of BINAP for 10 min at room temperature.

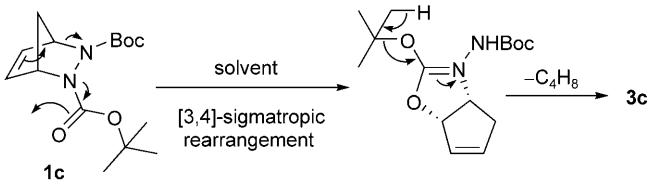


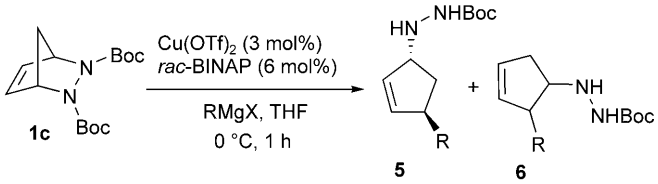
Figure 2. Plausible mechanism for the formation of 5,5-bicyclic carbazate **3c**.

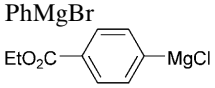
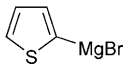
Cu(I)-phosphine catalyst might activate the nitrogen of the hydrazine promoting the rearrangement with the subsequent formation of volatile 2-methylpropene, as shown in Figure 2.[10]

Copper-catalyzed allylic alkylation with organometallic reagents represents a widely used synthetic strategy to introduce a carbon substituent on a molecule.[11] To our delight, after ensuring by TLC analysis that the $Cu(OTf)_2$-BINAP-catalyzed rearrangement had taken place (after *ca.* 10 min for **1c**), the subsequent one-pot addition of MeMgBr and EtMgBr to **1c** gave the corresponding monoprotected 1,4-adducts **5a** and **5b** with good S_N2'-regioselectivity and complete *anti*-stereoselectivity (entries 1 and 2, Table 2).[12] In order to verify the scope of the reaction, we next examined the addition of other Grignard reagents to **1c**. Interestingly, the use of allylmagnesium bromide, which is rarely used in copper-catalyzed allylic alkylations, gave the corresponding allylated cyclopentene **5c** very cleanly (entry 3). Also the use of benzylmagnesium bromide was satisfactory (entry 4). More sterically demanding reagents, such as *i*-PrMgCl, and the synthetic equivalent of the "CH_2OH" anion [i.e., $ClMgCH_2SiMe_2(i\text{-PrO})$], gave equally good yields of the corresponding adducts (entries 5 and 6).

Addition of aromatic Grignard reagents proceeded in good yields (entries 7 and 8), and also a heteroaromatic Grignard reagent was successfully employed, albeit with a not complete conversion of **3c** (entry 9). On the other hand, the addition of vinylmagnesium bromide was inefficient and delivered a complex mixture of products with a modest conversion (*ca.* 30% after 1 h at 0 °C , entry 10). It is worth mentioning that all compounds of type **5** were easily isolated in the pure state by chromatographic purification on silica gel, whereas regioisomeric adducts of type **6**, could not be obtained in a pure form. The *trans*-stereochemistry of adducts of type **5** was demonstrated by ^{1}H NMR analysis and comparison with related 1,4-substitued cyclopentene derivatives.[3,6] Evidently, an allylic carbazate of this kind is not able to direct the trajectory of the incoming organocopper nucleophile by coordination, and the displacement follows the canonical *anti*-stereoselective pathway.[14] All ring-opened adducts contained only one protecting group on the nitrogen distal to the cyclopentene ring, indicating that the decarboxylation of the 3-carbo-*tert*-butyloxy-carbazic acid (**A**), which is formed *in situ* after the allylic displacement of the carbazate, occurs spontaneously (Scheme 2).

Table 2. Copper-catalyzed one-pot rearrangement–alkylation of **1c** with Grignard reagents.[a]

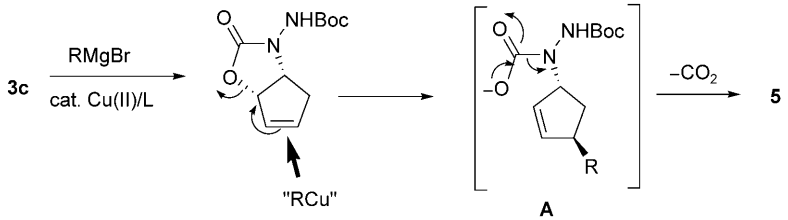


Entry	Grignard	Yield [%][b]	**5**/**6**[c]
1	MeMgBr	75 (**5a**)	87/13
2	EtMgBr	70 (**5b**)	86/14
3	allylMgBr	80 (**5c**)	83/17
4	$PhCH_2MgBr$	75 (**5d**)	81/19
5	$(i\text{-PrO})Me_2SiMeMgCl$	75 (**5e**)	82/18
6	*i*-PrMgCl	80 (**5f**)	86/14
7	PhMgBr	72 (**5g**)	83/17
8		85 (**5h**)	92/8
9		58 (**5i**)	85/15
10	vinylMgBr	complex mixture	

[a] *Conditions:* **1c** (1 equiv.), $Cu(OTf)_2$ (3 mol%), *rac*-BINAP (6 mol%) in THF at room temperature for 15 min, then RMgBr (3.0 equiv.) 0 °C for 1 h.

[b] Isolated yields of compound of type **5** after chromatographic purification on silica gel.

[c] Determined by ^{1}H NMR of the crude reaction mixture (see Supporting Information for details).



Scheme 2. Plausible mechanism for the formation of monoprotected adducts.

It is known that the hydrazine moiety can be converted by standard methods into valuable products, such as pyrazole derivatives,[15] 1,2,4-triazolo derivatives,[16] or into the corresponding amine by several reduction methods.[5i,17] In conclusion, replacement of the amide by urethane protecting groups, in particular with PG = Boc, inhibited the classical [3,3]-sigmatropic Lewis acid-catalyzed rearrangement of 2,3-diaza-[2.2.1]heptenes and gave a *cis*-fused 5,5-bicyclic allylic carbazate framework instead of the previously reported 5,6-bicyclic framework. This $Cu(OTf)_2$/(±)-BINAP-catalyzed rearrangement proved to be pivotal to obtain *trans*-1,4-disubstituted monoprotected hydrazinocyclopentenes by means of the subsequent one-pot allylic alkylation with Grignard reagents.

As an ample variety of Grignard reagents can be used, this very simple reaction protocol represents a useful and practical synthetic tool and nicely complements the known methods to access nitrogen-containing cyclopentenes.

Experimental Section

Typical Procedure: 1-(*tert*-Butoxycarbonyl)-2-{(1*R**, 4*R**)-4-[4-(ethoxycarbonyl)phenyl]cyclopent-2-en-1-yl)}hydrazine (5h)

Under argon atmosphere, a mixture of $Cu(OTf)_2$ (2.65 mg, 0.006 mmol) and racemic BINAP (7.50 mg, 0.012 mmol) in anhydrous THF (1.0 mL) was stirred for 10 min at room temperature. Cyclic hydrazine **1c** (59.2 mg, 0.2 mmol) in anhydrous THF (1.0 mL) was added, and the mixture was stirred at room temperature for *ca.* 15 min (TLC detection). The mixture was cooled at 0 °C, and then freshly prepared ArMgBr (*ca.* 1.0 M; 3 equiv, 0.6 mmol) was added. The mixture was allowed to react for 1 hour at 0 °C (100% conversion). The title compound was isolated by column chromatography eluting with hexanes/AcOEt (8:2), as an oil; yield: 59 mg (85%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.31–1.40 (m, 3H), 1.48 (s, 9H), 1.87 (ddd, J_1 = 5.0 Hz, J_2 = 7.5 Hz, J_3 = 12.5 Hz, 1H), 2.26 (ddd, J_1 = 3.3 Hz, J_2 = 11.5 Hz, J_3 = 11.7 Hz, 1H), 4.02–4.10 (m, 2H), 4.30–4.39 (m, 2H), 5.89–5.96 (m, 2H), 6.09–6.20 (br s, 1H), 7.12–7.19 (m, 2H); 7.90–7.97 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.3, 28.3, 39.1, 50.2, 60.8, 66.9, 80.8, 127.1, 128.5, 124.8, 132.3, 138.1, 150.6, 156.8 (w), 166.5; anal. calcd. for $C_{19}H_{26}N_2O_4$: C 65.87%, H 7.56%; found: C 65.89%, H 7.48%.

1-(*tert*-Butoxycarbonyl)-2-[(1*R**,4*R**)-4-methylcyclopent-2-en-1-yl]hydrazine (5a) (Table 2, entry 1)

Using the typical procedure, $Cu(OTf)_2$ (2.65 mg, 0.006 mmol), *rac*-BINAP (7.50 mg, 0.012 mmol), hydrazine **1c** (59.2 mg, 0.2 mmol) were used. After cooling at 0 °C MeMgBr (3.0 M in Et_2O; 0.2 mL, 0.6 mmol) was added. The mixture was allowed to stir for 1 hour at 0 °C (100% conversion). The product was isolated as an oil by column chromatography eluting with hexanes/AcOEt (8:2); yield: 32 mg (75%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.13 (d, J = 7.0 Hz, 3H), 1.49 (s, 9H), 1.59 (ddd, J_1 = 5.5 Hz, J_2 = 7.8 Hz, J_3 = 13.5 Hz, 1H), 1.93 (ddd, J_1 = 3.3 Hz, J_2 = 7.8 Hz, J_3 = 11.1 Hz, 1H), 2.78–2.91 (m, 1H), 4.08–4.17 (m, 1H), 5.51–5.58 (m, 1H), 5.80–5.89 (m, 1H), 6.06–6.19 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 21.0, 28.3, 37.4, 38.7, 66.7, 80.6, 129.3, 141.6, 156.5; anal. calcd. for $C_{11}H_{20}N_2O_2$: C 62.23%, H 9.50%; found: C 62.30%, H 9.48%.

1-(*tert*-Butoxycarbonyl)-2-[(1*R**,4*R**)-4-allylcyclopent-2-en-1-yl]hydrazine (5c) (Table 2, entry 3)

Using the typical procedure, $Cu(OTf)_2$ (2.65 mg, 0.006 mmol), *rac*-BINAP (7.50 mg, 0.012 mmol), hydrazine **1c** (59.2 mg, 0.2 mmol) were used. The mixture was cooled at 0 °C and then allylMgBr (1.0 M in Et_2O; 0.6 mL, 0.6 mmol) was added. The mixture was allowed to react for 1 hour at 0 °C (100% conversion). The product was isolated by column chromatography eluting with hexanes/AcOEt (8:2), as an oil; yield: 38 mg (80%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.48 (s, 9H), 1.67 (ddd, J_1 = 5.5 Hz, J_2 = 7.8 Hz, J_3 = 13.2 Hz, 1H), 1.88 (ddd, J_1 = 3.5 Hz, J_2 = 7.8 Hz, J_3 = 11.5 Hz, 1H), 2.01–2.11 (m, 2H), 2.82–2.92 (m, 1H), 3.82–4.01 (br s, 1H), 4.02–4.11 (m, 1H), 4.93–5.07 (m, 2H), 5.62–5.80 (m, 2H), 5.87–5.91 (m, 1H), 6.02–6.13 (br s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 28.3, 34.8, 39.9, 43.9, 66.5, 80.4, 115.8, 130.4, 136.8, 139.9, 147.6, 156.6 (w); anal. calcd. for $C_{13}H_{22}N_2O_2$: C 65.51%, H 9.30%; found: C 65.65%, H 9.25%.

Supporting Information

Additional experimental procedures and spectral data are available as Supporting Information.

Acknowledgements

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[8] a) The presence of rotamers in the ^{1}H and ^{13}C NMR analysis of *p*-Br-benzoyl- and *p*-nitrobenzoyl derivatives of compound **3c** (see compounds **7**–**9** in Supporting Information), and the formation of addition products of types **5** and **6** (not bearing the carbamate protection on the nitrogen linked to the cyclopentene framework, see Table 2 and Scheme 2), indicate the necessary occurrence of a 5,5-fused ring system. After the preparation of this manuscript, X-ray crystallographic proof on related derivatives was independently obtained by Mark Lautens and co-workers: b) A. Martins, S. Lemouzy, M. Lautens, *Org. Lett.* **2009**, *11*, 181–183.

[9] The reaction catalyzed by 3.0 mol% of $Cu(OTf)_2$, without added phosphine, was complete in *ca.* 3 h at room temperature. PPh_3 and Josiphos-type ligands gave a similar acceleration of the rearrangement. On the other hand, Monophos and triethyl phosphite delayed the rearrangement.

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