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[10] Borohydride, polymer-supported (borohydride on Amberlite IRA A-400, ~ 2.5 mmol g^{-1}) available from Aldrich.

[11] Available from Aldrich, dimethylaminopyridine, polymer-bound (cat. no. 35,988-2); poly(4-vinylpyridine) 2 % cross-linked (cat. no. 22,696-3).

[12] Despite the nonquantitative yield, no other material was detectable after filtration of the resin from the solution. We speculate that, due to the radical nature of the reaction, possible coupling of the starting material to the polymer resin has occurred.

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[14] Borohydride on polymer support (Amberlyst A-26 BH_4^- form, 1.5 – 4 mmol g^{-1}) available from Fluka (cat. no. 15595). The use of immobilised borohydride on Amberlite IRA 400[10] resulted in significant amounts of deprotected amino alcohol material. As an alternative, polymer-supported cyanoborohydride could be used, but in this case the reactions required more than 48 h.

[15] MP-TsOH 1.40 mmol g^{-1} available from Argonaut Technologies Inc. (cat. no. 800286; A15 was not effective in promoting this transformation).

[16] A fully automated Coherent Synthesis System microwave machine was used. This was supplied by Personal Chemistry: Hamnesplanaden 5, 753 19 Uppsala, Sweden; www.personalchemistry.com.

[17] *N*-(2-mercaptoethyl)aminomethyl polystyrene 1.2 mmol g^{-1} available from Nova Biochem. (cat. no. 01-64-0180).

[18] Carbonate on polymer support on IRA 900, ~ 3.5 mmol g^{-1} ($NaCO_3$) available from Fluka (cat. no. 21850).

[19] Polymer-bound triphenylphosphane ~ 3 mmol g^{-1} available from Fluka (cat. no. 93093).

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[21] Varian Chem. Elut Column (cat. no.1219-8007).

[22] (+)-Plicamine $[\alpha]_D = +77.5$ ($c = 0.867$ in MeOH); $[\alpha]_D^{lit} = +74.4$ ($c = 0.117$ in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.59$ (s, 1H; H-9), 7.08 (d, $J = 8.3$ Hz, 2H; H-2′ and H-6′), 6.73 (d, $J = 8.3$ Hz, 2H; H-3′ and H-5′), 6.49 (s, 1H; H-12), 6.01 (s, 2H; OCH_2O), 5.81 (d, $J = 10.1$ Hz, 1H; H-2), 5.36 (d, $J = 10.1$ Hz, 1H; H-1), 4.51 (ddd, $J = 13.8$, 8.3, 4.3 Hz, 1H; H-8′a), 4.06 (m, 1H; H-4a), 3.93 (s, 1H; H-6a), 3.87 (dd, $J = 12.3$, 4.3 Hz, 1H; H-4a), 3.51 (m, 1H; H-8′b), 3.44 (s, 3H; OMe), 2.93 (m, 2H; H-7′), 2.78 (s, 3H; NMe), 2.58 (m, 1H; H-3β), 1.39 ppm (m, 1H; H-3α); IR (neat): $\tilde{\nu}_{max} = 3292.7$, 2976.2, 2983.7, 1705.8, 1668.7, 1613.3, 1514.5, 1482.7, 1442.7, 1400.7, 1386.1, 1348.3, 1233.6, 1158.4, 1102.8, 1036.2, 931.9, 929.8 cm^{-1}; HR-MS calcd for $C_{26}H_{26}N_2O_6Na$: 485.1689; found 485.1694. Numbering from original paper concerning isolation see reference [5a].

[23] (−)-Plicamine $[\alpha]_D = -76.5$ ($c = 0.678$ in MeOH).

Catalytic Enantioselective Synthesis of β^2-Amino Acids**

Huw M. L. Davies* and Chandrasekar Venkataramani

In recent years the enantioselective synthesis of β-amino acids has been of considerable interest because β-amino acids[1] are useful precursors of β-peptides[2] and β-lactams.[2b, 3] Traditionally, the asymmetric synthesis of β^2-substituted amino acids has been achieved by using chiral auxiliaries in methods such as the alkylation of chiral enolates[4] and the acylation of metalated phenylacetonitrile with a chiral carbonyl chloride.[4c] Recently, highly enantioselective, L-proline-catalyzed, asymmetric Mannich-type reactions of *N*-PMP-protected (PMP = *p*-(MeO)C_6H_5) α-iminoethyl glyoxylate with aldehydes to generate functionalized β-amino acids was reported.[5] Herein we report a catalytic asymmetric synthesis of β^2-substituted amino acids. The crucial reaction is an asymmetric C–H activation of *N*-butoxycarbonyl (Boc)-protected methylamines by means of a [Rh_2(*S*-DOSP)$_4$] (**1**) induced C–H insertion [Eq. (1); TFA = trifluoroacetic acid].

Recently, numerous applications of the rhodium – carbenoid induced intermolecular C–H activation strategy in

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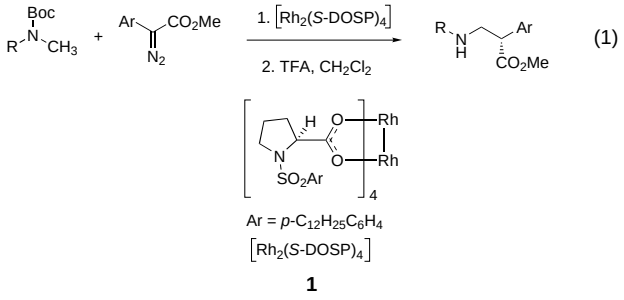
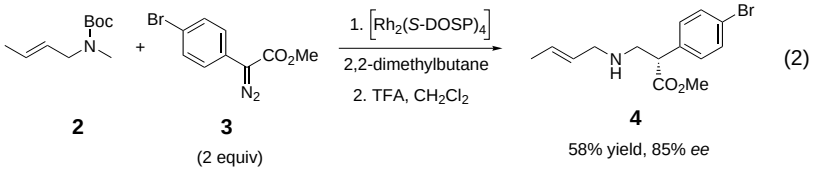
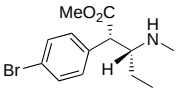


organic synthesis have been reported.[6] The results described here represent the first chemoselective C–H activations occurring at a methyl site. This reaction was discovered during studies on the development of the C–H activation of allylamines as a surrogate to the Mannich reaction.[7] Instead of the expected allylic C–H activation, the $[Rh_2(S\text{-DOSP})_4]$ (**1**)-catalyzed reaction of methyl-*p*-bromophenyldiazoacetate (**3**) with Boc-protected *N*-methylcrotylamine (**2**) formed an unexpected C–H activation product. After treatment of the crude reaction mixture with TFA to remove the Boc protecting group, the β-amino ester **4** was isolated in 58% yield and 85% *ee* [Eq. (2)]. As a selective insertion into a primary C–H



bond is unprecedented for intermolecular carbenoid-induced C–H activations, a full study to evaluate the scope of this reaction was undertaken.

Our earlier studies have demonstrated that the rhodium carbenoid derived from aryldiazoacetates behaves as a very sterically demanding reagent.[6a, 8] Presumably, this is the cause of the selective insertion into a methyl site over the electronically much more favorable allylic site. To explore this effect further, the C–H activation of a series of *N*-Boc-protected methylamines **5** were then examined (Table 1). In every case, except for the *N*-propyl derivative **5b**, a highly regioselective C–H insertion into the *N*-methyl site occurred to form after Boc deprotection the β-amino esters **6** in 57–62% yield. With **5b** a competing insertion into the methylene site also occurred to form **7** with very high diastereoselectivity (>94% *de*) but poor enantioselectivity (24% *ee*). The second N substituent has a dramatic effect on the enantioselectivity of the C–H activation with the *N*-benzyl derivative **5e** (95% *ee*) giving the best result.



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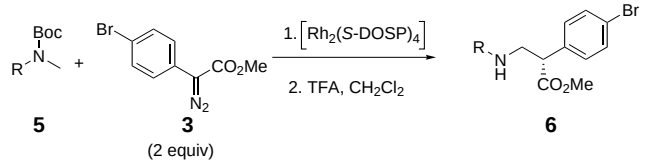
As all of the initial evaluations were carried out with Boc-protected amines, it was intriguing to determine if the C–H activation step was compatible with other common nitrogen protecting groups. As summarized in Table 2, the reaction was compatible with the benzyloxycarbonyl (Cbz) group but the yields were considerably lowered when the fluoren-9-ylmethoxycarbonyl (Fmoc) and 2-trimethylsilylethoxycarbonyl (Teoc) groups were used.

The intermolecular C–H insertion into **5e** is a general process for the synthesis of a range of β^2-substituted amino esters (Table 3). Various substituted phenyldiazoacetates can be used in this chemistry as well as naphthyldiazoacetate **9e**, thienyldiazoacetate **9g**, and styryldiazoacetate **9h**. The yields of the reactions are 55–67% and the enantioselectivities are 87–96% *ee*.

The discovery that the benzylamine **5e** is the optimum substrate for this chemistry is very attractive because the resulting products are readily converted to useful amino acids and

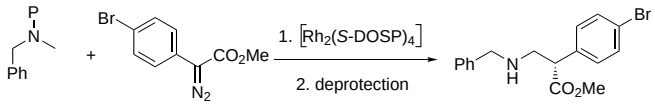
Table 1. The C–H activation of *N*-Boc-*N*-methylamines.



Compound	R	Yield [%][a]	*ee* [%]
5a	CH_3	61	31
5b	$CH_3CH_2CH_2$	46[b]	64
5c	$CH(CH_3)_2$	57	82
5d	$C(CH_3)_3$	58[c]	54
5e	$C_6H_5CH_2$	62	95
5f	$(CH_3)_2C{=}CHCH_2$	62	87
5g	*trans*-PhC=CHCH$_2$	60	87

[a] Yield of isolated product. [b] 8% of **7** was also formed (>94% *de*, 24% *ee*). [c] Isolated with Boc group.

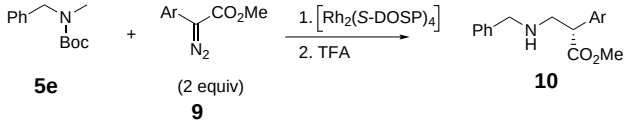
Table 2. Comparison of the effects of different nitrogen protecting groups on the C–H activation step.



Compound	P	Yield [%][a]	*ee* [%]
8a	Cbz	67	90
8b	Fmoc	21	69
8c	Teoc	26	94

[a] Yield of isolated product.

Table 3. The C–H activation of *N*-Boc-*N*-benzyl-*N*-methylamine.



Compound	Ar	Yield [%][a]	*ee* [%]
9a	C_6H_5	67	96
9b	4-$CF_3C_6H_4$	55	92
9c	4-$OCH_3C_6H_4$	61	92
9d	4-$CH_3C_6H_4$	66	95
9e	2-naphthyl	55	87
9f	4-ClC_6H_4	62	96
9g	3-thienyl	58	90
9h	$C_6H_5CH{=}CH_2$	56[b]	96

[a] Yield of isolated product. [b] Isolated with Boc group.

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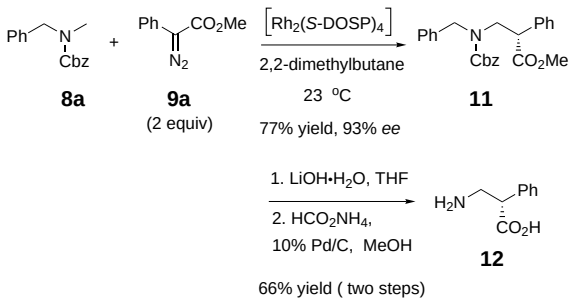
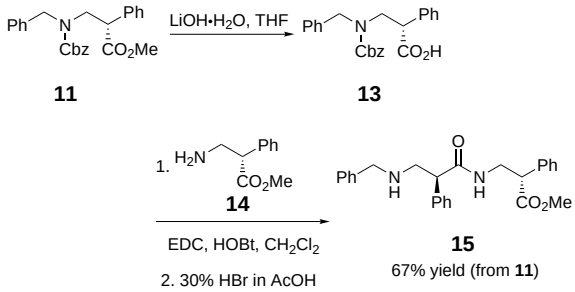
peptides. $[Rh_2(S\text{-DOSP})_4]$-catalyzed decomposition of **9a** in the presence of **8a** gave the C–H insertion product **11** in 77% yield and 93% *ee*. Cleavage of the methyl ester (**11**) using $LiOH \cdot H_2O$ in THF, followed by transfer hydrogenation provided α-phenyl-β-alanine **12** in 66% yield [Eq. (3)]. The



(3)

absolute stereochemistry was determined to be *S* by comparison of the sign of optical rotation of **12** ($[\alpha]_{25}^{D} = -87.6$, $c = 0.13$, H_2O) which was found to be opposite that of the literature value[9] ($[\alpha]_{25}^{D} = +85$, $c = 0.2$, H_2O) for the *R* isomer. Application of the predictive C–H insertion model correctly predicts the observed stereochemistry.[6d,h, 8b]

The products would also be applicable to the synthesis of β-peptides as illustrated in the synthesis of the dipeptide **15** [Eq. (4)]. Hydrolysis of **11** gave the acid **13**, which was coupled (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC), 1-hydroxybenzotriazole (HOBt)) with the amine **14** (prepared from **11** by hydrogenation) to give the dipeptide **15** in 67% yield.



(4)

In summary, these preliminary studies demonstrate that the intermolecular C–H insertions of carbenoids derived from aryldiazoacetates catalyzed by $[Rh_2(S\text{-DOSP})_4]$ is an attractive method for the asymmetric synthesis of substituted β-amino acids. The reaction proceeds with good chemo- and enantioselectivity and demonstrates the remarkable steric control that is possible with these rhodium–carbenoid intermediates. Further studies to explore the full scope of this chemistry are currently underway.

Experimental Section

Representative example (**6e**): Methyl 4-bromophenyldiazoacetate (**3**) (0.23 g, 0.90 mmol) in 2,2-dimethylbutane (7 mL) was added dropwise over 3 h using a syringe pump to a solution of $[Rh_2(S\text{-DOSP})_4]$ (17 mg, 0.01mmol) and **5e** (0.100 g, 0.45 mmol) in 2,2-dimethylbutane (5 mL). After the addition, the resulting solution was stirred at 23 °C for 1 h. The solvent was removed under reduced pressure, and the residue was reconstituted in CH_2Cl_2 (10 mL) and TFA (0.2 mL, 2.26 mmol) and stirred for 16 h at 23 °C. The solution was concentrated in vacuo, and the residue was dissolved in Et_2O (20 mL) and extracted with 10% HCl (3×15 mL). The combined aqueous layers were basified ($NaHCO_3$, 1M NaOH to pH 8–9) and extracted with EtOAc (3×15 mL). The combined organic layers were washed with water (1×15 mL), brine (1×20 mL), and dried over Na_2SO_4. The product was purified by flash chromatography (SiO_2, Et_2O/pentane/NEt_3 = 25:35:2) to give the title compound **6e** (97 mg, 0.28 mmol; 62% yield). $[\alpha]_{25}^{D} = -44.7°$ ($c = 1.36$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.44$ (d, $J = 7.5$ Hz, 2H), 7.32–7.22 (m, 5H), 7.16 (d, $J = 7.0$ Hz, 2H), 3.8 (s, 2H), 3.77 (m, 1H), 3.66 (s, 3H), 3.26 (m, 1H), 2.91 ppm (dd, $J = 6.5$, 11.5 Hz, 1H); ^{13}C NMR (DEPT) (125 MHz, $CDCl_3$): $\delta = 173.1$ (C), 139.8 (C), 136.1 (C), 131.8 (CH), 129.7 (CH), 128.3 (CH), 127.9 (CH), 126.9 (CH), 121.4 (CH), 53.5 (CH_2), 52.1 (CH_3), 51.7 (CH_2), 51.5 ppm (CH); IR (neat): $\tilde{\nu} = 3328$, 3024, 2948, 2844, 1730 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{18}NBrO_2$: C 58.63, H 5.21, N 4.02; found: C 58.76, H 5.25, N 4.06. To measure the enantiomeric excess of **6e**, it was converted to its trifluoroacetamide. Acylation of a small sample of the free amine from above with trifluoroacetic anhydride (TFAA) and CH_2Cl_2 followed by flash chromatography (SiO_2, Et_2O/pentane = 15:85) gave the amide in 95% *ee* (HPLC, Chiralcel-AD-RH column, 5.0% 2-propanol in hexanes, 1.0 mL min^{-1}, 1 mg mL^{-1}, $t_R = 4.62$ (major) and 8.16 (minor) min, UV 254 nm).

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