Enantioselective synthesis of β-amino esters and its application to the synthesis of the enantiomers of the antidepressant Venlafaxine†

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Received (in Bloomington, IN, USA) 6th April 2006, Accepted 21st May 2006
First published as an Advance Article on the web 14th June 2006
DOI: 10.1039/b605047f

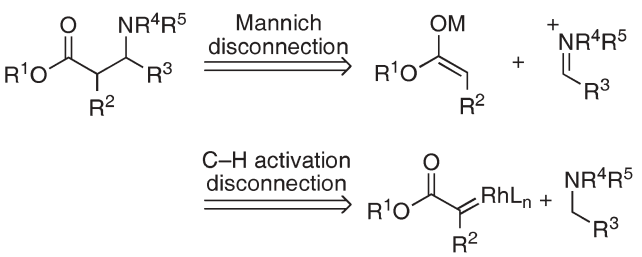
β-Amino esters are readily formed from the rhodium(II) prolinate-catalyzed intermolecular C–H insertion between methyl aryldiazoacetates and a bis-silyl protected methylamine.

The development of practical C–H activation methods are of considerable current interest because they can lead to new strategic reactions for synthesis. One effective C–H activation process has been the C–H insertion chemistry of metal carbenoids. In recent years, donor/acceptor-substituted carbenoids have been shown to be capable of highly regioselective and stereoselective C–H activation.[1] C–H bonds adjacent to nitrogen are especially favorable sites for functionalization, and from a strategic perspective this is a significant transformation because it is a surrogate of the Mannich reaction (Scheme 1).[2]

Over the last few years, we have been exploring what types of nitrogen functionality are compatible with intermolecular C–H activation chemistry. A site that is too nucleophilic will tend to react with the carbenoid or poison the catalyst,[3] while unprotected N–H bonds will be prone to N–H insertion.[4] So far, we have found that *N*-Boc protected cyclic amines **1**,[2a,c,d] *N*-Boc-*N*-alkyl-*N*-methylamines **2**[2b] and *N*,*N*-dimethylanilines **3**[2e] are effective substrates for intermolecular C–H activation (Fig. 1).[2]

In this paper, we describe how *N*-methyl-1-aza-2,5-disilacyclopentane (**4**)[5] (Fig. 2) is a useful substrate for the C–H activation chemistry. It can be effectively used for the direct enantioselective synthesis of β-amino esters **5**,[6] and in a three-step synthesis of the enantiomers of the antidepressant Venlafaxine (**6**).[7]

The dominant chiral catalyst for enantioselective reactions of donor/acceptor-substituted carbenoids has been the dirhodium(II) prolinate, Rh_2(*S*-DOSP)$_4$.[8] In order to explore the feasibility of the Rh_2(*S*-DOSP)$_4$-catalyzed reactions of aryldiazoacetates with



Scheme 1

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† Electronic Supplementary Information (ESI) available: Experimental details for the synthesis of all new compounds. See DOI: 10.1039/b605047f

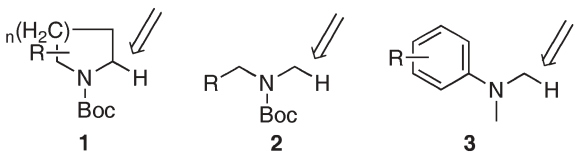


Fig. 1 Protected amines capable of C–H activation.

silyl-protected methylamine (**4**), a systematic study was conducted by using phenyldiazoacetate (**7a**) as the carbenoid source (Scheme 2). A major advantage of using the bis-silyl protecting group is that it is stable under carbenoid reaction conditions and appears to sterically protect the amino group from the electrophilic carbenoid. Under mildly acidic conditions, however, the protecting group is very labile and the β-amino ester is released and readily isolated as its hydrochloride salt. When the bis-silylamine **4** was

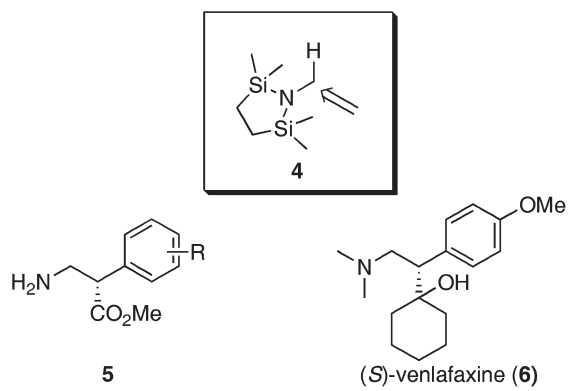
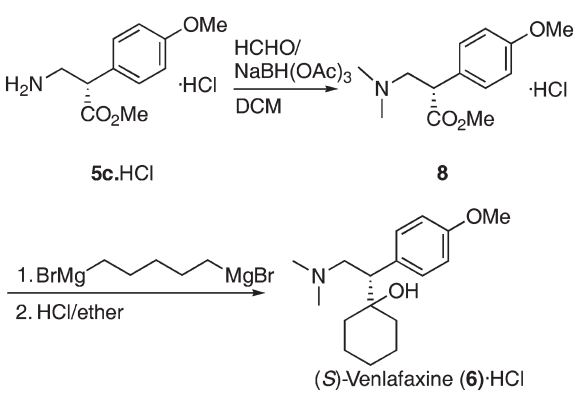
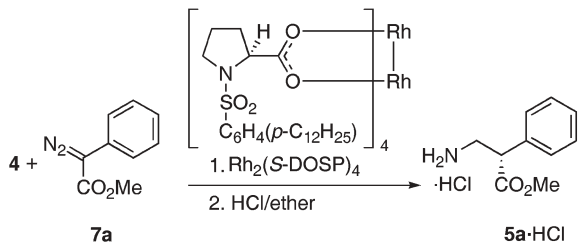


Fig. 2 *N*-methyl-1-aza-2,5-disilacyclopentane (**4**) as a substrate for C–H activation.



Scheme 2

Table 1 Optimization studies for C–H functionalization of **4**



Entry	Equiv. **7a**	Temperature/°C	Catalyst loading (%)	Yield (%)[a]	ee (%)
(a)	2	25	1	73	84
(b)	2	−40	1	68	93
(c)	0.5	−40	2	53	97

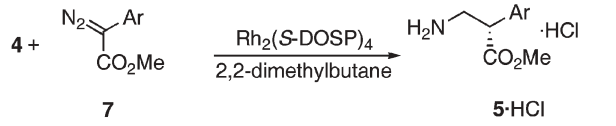
[a] Yield is based on the limiting reagent.

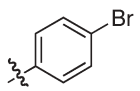
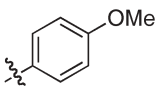
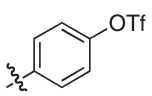
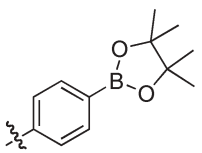
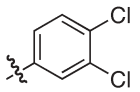
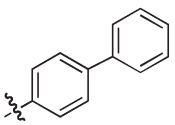
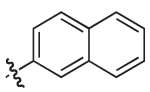
used as the limiting reagent, the reaction, conducted at room temperature, gave the β-amino ester **5a** in 73% yield and 84% ee (Table 1, entry a). The enantioinduction could be improved to 93% ee, without much loss in yield by conducting the reaction at −40 °C (Table 1, entry b). Even higher enantioinduction (97% ee) could be obtained by making **7a** the limiting reagent, but the yield was lower (53%) in this case (Table 1, entry c).

Having developed optimized conditions for the C–H activation chemistry, the reaction was then extended to a series of aryldiazoacetates (Table 2). The β-amino esters were isolated as their hydrochloride salts, which eliminated the need for chromatographic purification. In the case of aryldiazoacetates lacking electron donating groups, the reactions were conducted at −40 °C with an excess of protected *N*-methylamine **4** (conditions A). The carbenoids from more electron rich aryldiazoacetates, such as **7c** and **7e**, are less reactive and their reactions are best conducted at 0 °C with the slow addition of a two-fold excess of the aryldiazoacetate (conditions B). The β-amino esters **5** are produced in moderate to high enantioselectivity (65–97% ee). Particularly interesting are the reactions with the bromide **7b**, triflate **7d** or boronate **7e** derivatives, which lead to the possibility of making various analogs through Suzuki coupling.

After establishing the C–H functionalization of **4** as an effective method for the synthesis of β-amino esters, the methodology was extended to the enantioselective synthesis of the antidepressant Venlafaxine (**6**) (Effexor™). This pharmaceutical agent has been commercialized as a racemic mixture, even though both enantiomers have significant biological activity. (*S*)-**6** is a relatively selective serotonin reuptake inhibitor, while (*R*)-**6** is more selective for the norepinephrine transporter.[7a] The required C–H insertion product, **5c**, was generated in 62% yield and 93% ee. The published Eschweiler–Clarke conditions[7a] for the *N*,*N*-dimethylation of racemic **5c** to **8** were not suitable because epimerization occurred under the rather harsh conditions. $HCHO/NaBH(OAc)_3$ was found to be a suitable alternative, as it resulted in the effective conversion of **5c** to **8** in 82% yield at room temperature with no loss of ee being found. Finally, conversion of **8** to (*S*)-Venlafaxine was achieved by reaction with pentyl-1,5-dimagnesium bromide.[9] The optimum conditions required slow parallel addition of solutions of both the Grignard reagent and the ester to the reaction vessel. After the work-up of the reaction, formation of the HCl salt and enrichment by recrystallization, (*S*)-**6** was obtained in 49% yield and 99% ee. (*R*)-**6** was prepared in similar way from a reaction sequence beginning with a Rh_2(*R*-DOSP)$_4$-catalyzed reaction.

Table 2 Enantioselective synthesis of β-amino esters **5**[a]



Compound	Ar	Yield (%) (Conditions)	ee (%)
a		53 (A)	97
b		53 (A)	94
c		62 (B)	93
d		63 (B)	85
e		55 (B)	71
f		30 (A)	65
g		54 (A)	95
h		75 (B)	80

[a] Conditions A: −40 °C, 0.5 equiv. **7**, 2% catalyst, 2 h addition. Conditions B: 0 °C, 2 equiv. **7**, 2% catalyst, 5 h addition.

In summary, the C–H insertion reactions of the bis-silylmethylamine **4** with various aryldiazoacetates afforded β-amino esters in good yields and with high enantioselectivity. Using this method, the enantiomers of the antidepressant Venlafaxine were synthesized in three simple steps with high enantioselectivity.

This work was supported by the National Institutes of Health (DA15225 and DA06634) and the National Science Foundation (CHE-030536).

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