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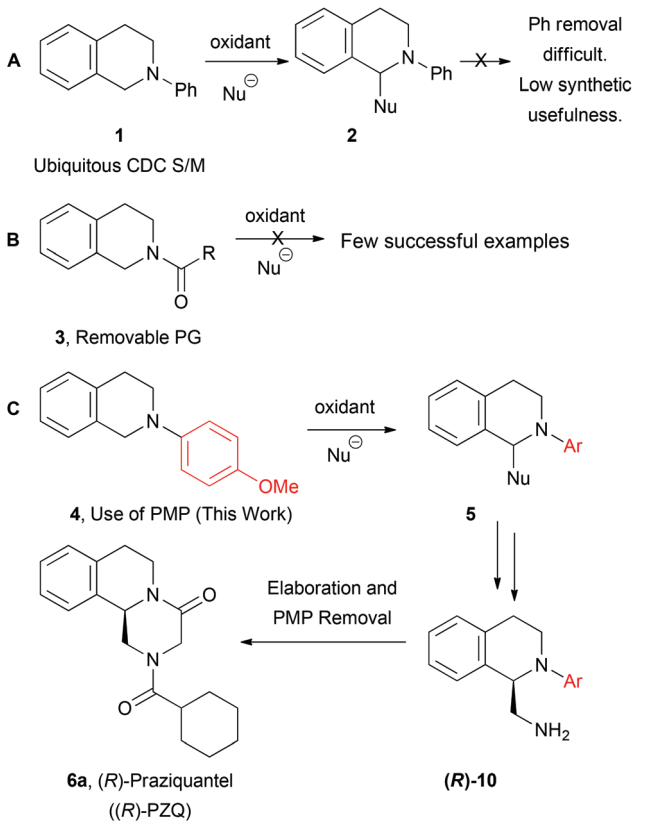
Enhancing the usefulness of cross dehydrogenative coupling reactions with a removable protecting group†

Althea S.-K. Tsang,[a] Katrin Ingram,[b] Jennifer Keiser,[b] D. Brynn Hibbert[c] and Matthew H. Todd*[a]

A removable protecting group has been identified that allows the products of widely-used cross dehydrogenative couplings to be synthetically elaborated. The method can be used with enantiopure amines with no loss of enantiomeric excess. The methodology is exemplified by a new synthesis of enantiopure praziquantel, the drug used in the treatment of millions of people suffering from the neglected tropical disease, schistosomiasis.

The methodology of "cross dehydrogenative coupling" (CDC) reactions has grown remarkably over the past five years, with successful reaction conditions and a wide scope of coupling partners now well explored.[1] These methodologies typically involve bond formation adjacent to a heteroatom, in particular adjacent to a protected nitrogen atom where protection is necessary to avoid amine oxidation. In essentially every published case (at least 60 separate reports to date) the nitrogen atom is protected with a phenyl ring (**1**, Scheme 1A). One of the drawbacks of this approach is that removing the phenyl ring is difficult, and hence further functionalisation of CDC reaction products is seldom pursued. Greater synthetic usefulness of CDC protocols would be demonstrated if the *N*-protecting group could be removed and the products elaborated. An obvious solution is to use a more labile protecting group such as a carbamate (*e.g.*, Boc, Troc and Cbz, **3**, Scheme 1B) but there are few such methodologies describing successful CDC reactions in the published literature.[2] We herein show that using a *para*-methoxyphenyl (PMP) substituted amine (**4**, Scheme 1C) facilitates the desired CDC reaction, after which deprotection allows for further elaboration of the unmasked amine; the conditions permit the synthesis of enantioenriched CDC products. The effectiveness of this method is demonstrated through a new synthesis of one of the world's most widely used anthelminthic drugs (praziquantel (PZQ), **6a**) as a single enantiomer, as well as a novel analog now accessible with this chemistry.



Scheme 1 Cross dehydrogenative coupling (CDC) reactions with different protecting group strategies.

We previously discovered a fast and high-yielding CDC reaction between *N*-phenyl tetrahydroisoquinoline and nitromethane that gives the nitroamine **7** (Scheme 2).[3] This oxidative coupling reaction has been reported with variations by others, but never with any other protecting group on the

[a]*School of Chemistry, The University of Sydney, Sydney, New South Wales, Australia. E-mail: matthew.todd@sydney.edu.au; Fax: +61 2 9351 3329; Tel: +61 2 9351 2180*
[b]*Swiss Tropical and Public Health Institute and University of Basel, Basel, Switzerland*
[c]*School of Chemistry, University of New South Wales, Sydney, New South Wales, Australia*

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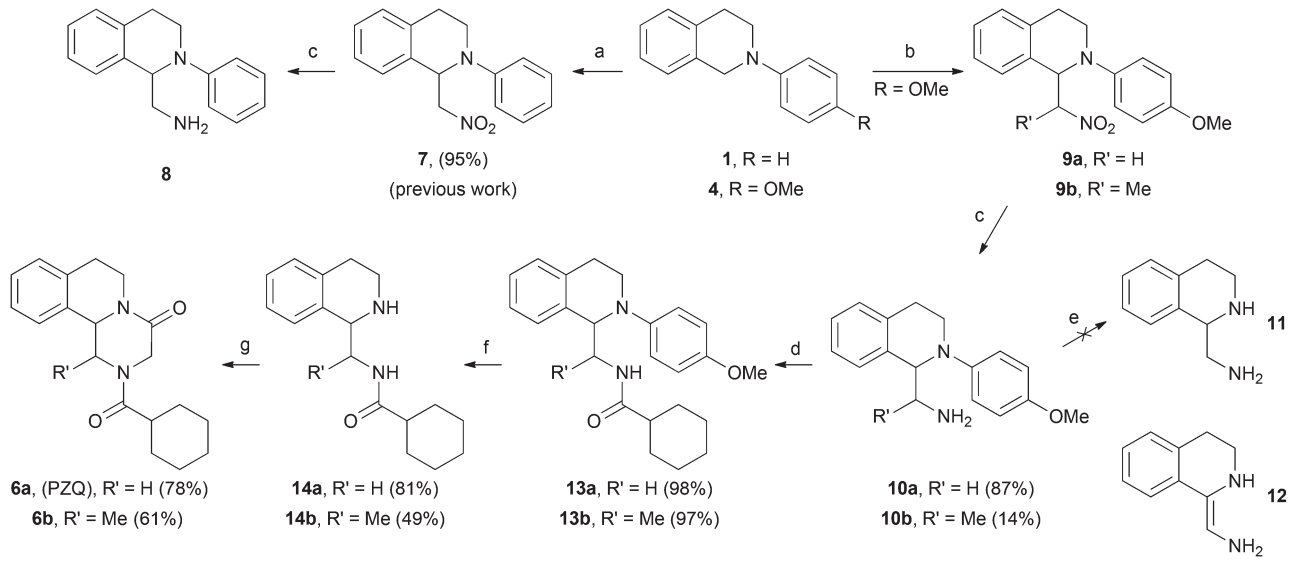

Scheme 2 Synthetic elaboration of CDC reaction products through the use of a PMP group, exemplified by the synthesis of praziquantel. *Reagents and conditions*: (a) iodoanisole, CuI, K_3PO_4, ethylene glycol, isopropanol, 80 °C, 24 h; (b) DDQ, nitromethane for **9a** or nitroethane for **9b**, rt, 5 min; (c) RANEY® nickel, H_2, 4 h, rt; (d) cyclohexane carbonyl chloride, DMAP, Et_3N, CH_2Cl_2, 0 °C, 4 h; (e) $(NH_4)_2Ce(NO_3)_6$, MeCN–H_2O, 0 °C, 5 min; (f) chloroacetyl chloride, NaOH, CH_2Cl_2, rt, 30 min, then TEBAC, reflux, 2 h.

nitrogen atom; this is unfortunate since synthetic elaboration of the products would lead to a range of versatile new chiral vicinal diamines, similar to those accessible with Reissert chemistry but without the hazards associated with the use of cyanide. Access to such compounds has recently been achieved through the aza-Henry reaction of dihydroisoquinoline.[4] While we previously showed reduction of the beta-nitroamine to the protected diamine (**8**) was possible, the products could not be taken on further. The phenyl substituent promotes the CDC reaction but essentially acts as a protecting group that is too effective in subsequent steps. These problems may be overcome with the simple expedient of using instead the PMP-protected starting material (**4**), derivable from tetrahydroisoquinoline using a copper-catalysed arylation.[5] The CDC reaction with nitromethane proceeds with the same efficiency and speed as the original reaction to give the nitroamine **9a**. The reduction of the nitro group to the amine, not a trivial operation for beta-nitroamines[6] could be effected with RANEY® nickel in methanolic ammonia at room temperature in excellent yield.

Access to more diverse and interesting derivatives required the removal of the protecting group. It was expected that oxidative deprotection of **10a** to diamine **11** would be problematic due to the reactivity of the primary amine. Use of $(NH_4)_2Ce(NO_3)_6$ (ceric ammonium nitrate, CAN) gave the corresponding enamine (**12**). To moderate the reactivity of the amine it was converted to an amide; with one eye on an eventual synthesis of PZQ the amine was reacted with cyclohexane carbonyl chloride to give **13a**. Literature procedures describing the removal of *para*-methoxyphenyl groups from nitrogen centres use wet solvents under oxidative conditions for the hydrolysis of the electron-rich ring from the heteroatom, giving free amines[7] or amides[7a] and the benzoquinone fragment. We found that a slight excess of CAN in aqueous acetonitrile efficiently removed the PMP group, giving the free amine **14a** in good yield. Subsequent cyclisation with chloroacetyl chloride under phase transfer conditions[8] was also successful, giving praziquantel **6a** in a 45% yield overall, representing one of the most efficient syntheses of this molecule to date.‡

The oxidative coupling of nitromethane to aryltetrahydroisoquinolines is versatile in that nitromethane can be replaced with other nitroalkanes. As an example, nitroethane was employed in the synthetic scheme just described. While the initial coupling was highly efficient, subsequent reduction of the beta-nitroamine under the same conditions was only partially successful with a low (unoptimised) yield of the desired amine being obtained; the majority of isolated material was the uncoupled starting material **4**. Subsequent acylation of the amine, deprotection and cyclisation were successful, giving PZQ analog **6b**. This structure is significant. PZQ has been in constant use for the treatment of the neglected tropical disease schistosomiasis (bilharziosis) since its discovery in the 1970s, and there have been considerable efforts at analog synthesis given PZQ's status as the preferred drug for the treatment of the more than 200 million people currently infected with this disease.[10] Yet no analogs have ever been reported with variation in the 9-position. Confirmation of the structure of **6b** was achieved by 2D NOESY, COSY, HMBC and HSQC NMR spectroscopy (and by comparison to similar data for **6a**, from the literature and obtained here), specifically permitting the assignment of signals representing the protons at C^1, C^9 and C^{10} and C^{11} (see ESI†). Notably, the ^{1}H NMR spectrum of **6b** (Fig. 1) showed an unusual difference in chemical shift of more than 1 ppm for the two protons attached to carbon C^3. The analog **6b** was generated with a diastereomeric ratio of 82 : 18 according to the ratio of the relevant peaks in the compound's ^{1}H NMR spectrum.§

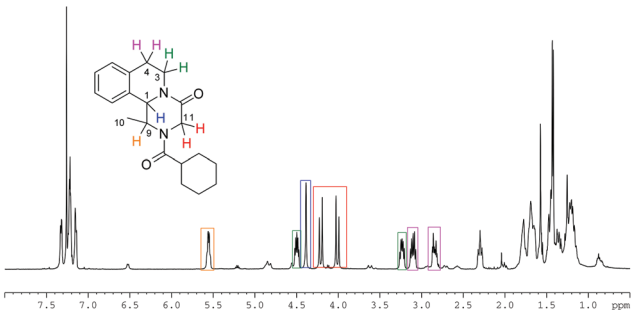

Fig. 1 ^{1}H NMR spectrum of compound **6b**, showing assignments of key proton environments derived from 2D experiments and the unusual difference in chemical shift of protons attached to carbon C^3 (highlighted in green).

A sample of this novel 9-methyl PZQ analog was biologically evaluated against adult schistosomes but was found to be inactive (IC_{50} > 25 μg mL^{-1}, ESI†). Though the sample is obviously a mixture of four isomeric compounds, this result implies that methylation at the 9-position is not tolerated, adding to the literature on the high sensitivity of this compound to structural change.[11]

The facile synthesis and handling of chiral primary amine **10a** suggested this compound could be resolved, which would broaden the usefulness of these CDC reaction products, particularly if the subsequent removal of the PMP group did not epimerise the benzylic stereocentre. A search for a suitable resolving agent began with a derivative of tartaric acid.[12] To navigate the multiple factors involved in optimising a resolution, a statistically-based Design of Experiments (DoE) protocol was used.[13] A Box–Behnken design was adopted as an efficient method for a system in which it can be assumed that the optimum result is within the experimental factor space defined by the choice of variable extremes. The factors chosen in this DoE search were concentration of amine (0.05 to 0.2 M wrt amine), solvent ratio (1 : 1 to 6 : 1 isopropanol–water), time (6 to 24 h) and temperature (0 °C to rt). A three-level Box–Behnken design (*i.e.*, three different values for each variable) incorporating these factors was implemented (see ESI†) giving optimal values (5 : 1 isopropanol–water, at temperatures between 12 and 20 °C for 24 h) for the resolution of compound **8**.

Subjecting amine **10a** to these resolution conditions gave an enantioenrichment of 62% ee which could be increased to 95% ee by recrystallisation from minimal 8 : 1 isopropanol–water. Pleasingly when this enantioenriched sampled was subjected to the PMP removal no loss of enantiomeric excess was observed. To date, literature examples of PMP amine deprotections on chiral substrates have suggested, but not conclusively shown, retention of stereochemical integrity.[14]

The amine could be taken through to enantiopure PZQ, upon which it was found that the (*S*)-enantiomer had been produced. This enantiomer is the undesirable, biologically inactive enantiomer of the drug that is responsible for the racemate's bitter taste.[15] Repetition of the procedure using the antipode of the resolving agent allowed for the synthesis of the active (*R*)-enantiomer of PZQ in 97% ee. The preparation of this enantiopure compound, a stated research goal of the World Health Organisation, was recently reported *via* a different resolution starting from the racemate.[12]

Conclusions

The present approach extends the already-powerful CDC methodology through the use of the PMP protecting group. This modification preserves the high-yielding one-pot nature of the coupling reaction, but allows for the downstream elaboration of the CDC products. In the event that chiral, enantioenriched amines are employed, it has been shown that protecting group removal does not compromise the enantiomeric excess of the CDC reaction product, as illustrated by a new synthesis of enantioenriched praziquantel, an important drug. Given the ease of protection and deprotection involved in the use of the PMP group in CDC reactions, it is expected that its adoption in preference to the phenyl group will lead to a broader range of applications for CDC reactions in synthesis.

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Notes and references

‡Characterisation was in agreement with the literature.[9]

§The ratio was found to be 72 : 28 according to the integrals of peaks obtained in the HPLC spectrum at 270 nm, suggesting that the diastereoisomers probably have different extinction coefficients.

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