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A Stereospecific Ruthenium-Catalyzed Allylic Alkylation**

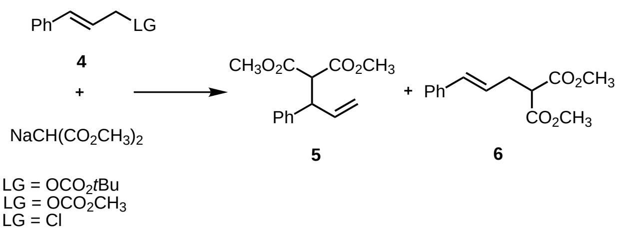
Barry M. Trost,* Pierre L. Fraisse, and Zachary T. Ball

Metal-catalyzed allylic alkylations provide a powerful tool for the construction of complex molecules. One of the benefits of such substitutions is the prospect that the regioselectivity with unsymmetrical allyl substrates can be controlled by the catalyst rather than the position of the allylic substituent serving as the leaving group. Palladium-catalyzed allylic alkylations normally favor nucleophilic addition to the less substituted allyl terminus although ligands can influence this selectivity.[1] Early results demonstrate the effectiveness of Mo[3] and W[4] catalysts and, more recently, their ability to induce enantioselectivity.[5] Such catalysts normally do not work with heteroatom nucleophiles. Iridium catalysts have been reported to favor attack on the more substituted carbon with a carbon—and most recently nitrogen—nucleophile, but the use of an oxygen nucleophile like phenol has not been reported.[6] Rhodium catalysis has proven to be very interesting in that the regioselectivity of the substitution is determined by the position of the leaving group.[7] Herein, we report our preliminary observations that the ruthenium-catalyzed reaction favors attack at the more substituted carbon atom regardless of the regioisomeric nature of the substrate and does so with complete retention of enantiomeric purity when a chiral scalemic substrate is employed. This study has led to a facile synthetic strategy to antidepressants like fluoxetine,[8] the active ingredient of prozac, from ephedrine.

Pioneering work in ruthenium-catalyzed allylic alkylation by Watanabe et al. with the [Ru(cod)(cot)] (cod = 1,5-cyclooctadiene; cot = 1,3,5-cyclooctatriene) complex has indicated a bias for attack at the more substituted terminus with some nucleophiles, although only a 50:50 regioisomeric mixture was obtained by using a cinnamyl carbonate and malonate anion.[9] [CpRu(cod)Cl][10] (**1**) and $[CpRu(PPh_3)_2Cl]$[11] (**2**) have been employed together with heteroatom nucleophiles, but the regioselectivity has not been satisfactorily addressed.

Our recent work on cyclocondensations of allenes and vinyl ketones using $[CpRu(NCCH_3)_3]PF_6$ (**3**) induced us to examine this complex as a catalyst for regioselective allylic alkylation.

We chose the reaction shown in Equation (1) as a standard. In contrast to the earlier reports in which **1** or **2** were used and which required elevated temperatures, complex **3** effected the reaction of carbonate **4a** at ambient temperature in DMF to give a 1:2 ratio of **5**:**6** in nearly quantitative yield. Attempts to increase this selectivity by varying the reaction conditions failed and thus we examined changes in the ligand. We reasoned that a more sterically demanding catalyst might favor the monosubstituted olefin adduct initially formed from "branched" attack to afford **5**. Under identical conditions with carbonate **4a**, $[Cp^*Ru(NCCH_3)_3]PF_6$ (**7**) ($Cp^* = \eta^5\text{-}C_5Me_5$) gave a 9:1 ratio of **5**:**6** (96% yield) in 2 h. In acetone, the selectivity increased to 19:1 (quantitative yield). Reactions of the methyl carbonate **4b** are generally faster. Indeed, in DMF within 30 min, a quantitative yield of alkylation products was obtained in a 14:1 ratio of **5**:**6** with only 1 mol% of catalyst **7**.



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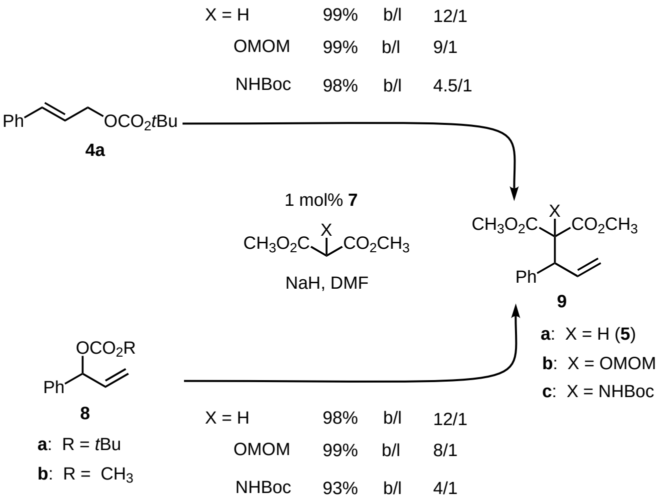
Cinnamyl chlorides (**4c**) are also effective electrophiles. Although poor regioselectivity is observed at ambient temperature, at −40 °C in DMF, a quantitative yield of virtually pure **5** (**5**:**6** 110:1) was obtained.

The regioselectivity as a function of the regioisomeric allylic carbonates **4a** and **8** was examined with a series of malonates [Eq. (2); b = branched, l = linear]. Very similar results were obtained with three different malonates, whereby the branched product **9** was strongly favored. To a first approximation these results support the postulate of a π-allylruthenium intermediate. Catalyst-controlled regioselectivity is further demonstrated for an unsymmetrical, disubstituted allyl unit [Eq. (3)], for which excellent preference for the benzylic position is observed for an allylic carbonate of opposite regiochemistry. Unfortunately, direct extension to α-cyanocyclopentanone led to a sluggish reaction (30% conversion after 4 h) and poor regioselectivity (b/l 1.6:1) [Eq. (4), path a]. This problem was resolved in a most gratifying fashion—by simply running the reaction without solvent using tri-*n*-butylamine as base and with **8** as the substrate [Eq. (4), path b]. These neat conditions proved general for bulkier nucleophiles, and Equation (5) illustrates the applicability of heteroaryl substrates **13**. Notably, diastereoselection has not been observed for the unsymmetrical β-keto ester nucleophiles. Yields given are for an approximately 1:1 mixture of (sometimes separable) diastereomers.



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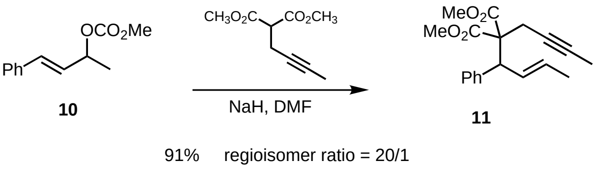
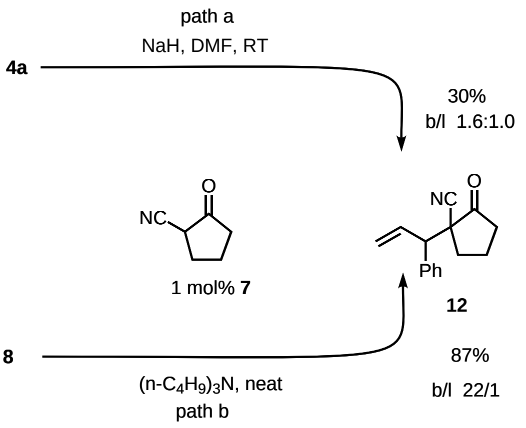


(3)

Having established the involvement of a functional equivalent of a π-allylruthenium intermediate, we examined the stereochemistry of the substitution by using chiral substrate **8** of high enantiopurity [Eq. (6)]. Starting with (*S*)-**8a** of 94% *ee* gave (*R*)-**9a** of 94% *ee*, therefore constituting complete chirality transfer (CT). The absolute configuration was established by comparison with a known sample. Similarly, starting with the enantiomeric substrate (*R*)-**8b** of 99% *ee* with the amidomalonate gave the epimeric product (*R*)-**9c** of 99% *ee*, again constituting 100% CT. Thus, ionization occurs to generate cleanly only one enantiomeric π-allylruthenium complex that does not equilibrate under the reaction conditions. We next sought to extend the scope of our enantiospecific alkylation to O-nucleophiles in the context of the synthesis of the antidepressants (*R*)-fluoxetine[8] and (*R*)-tomoxetine from (*S*)-ephedrine as shown in Scheme 1.[12] The starting allyl alcohol was available by Hoffmann elimination of the quaternary ammonium salt derived from ephedrine using strong base.[13] Both enantiomers of the allyl alcohol are readily available from the corresponding commercial ephedrine. The free phenol was not a satisfactory nucleophile, but its silyl ether in the presence of a catalytic amount of a



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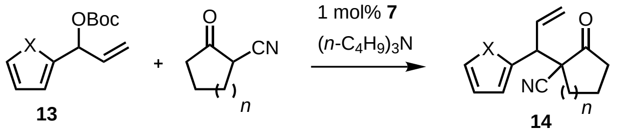
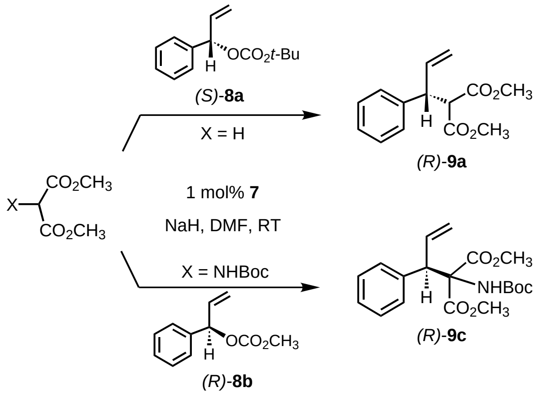


(5)

a: X = O
b: X = S

X	*n*	%	b/l
O	1	86	70/1
O	2	85	16/1
S	1	98	100/1
S	2	88	13/1



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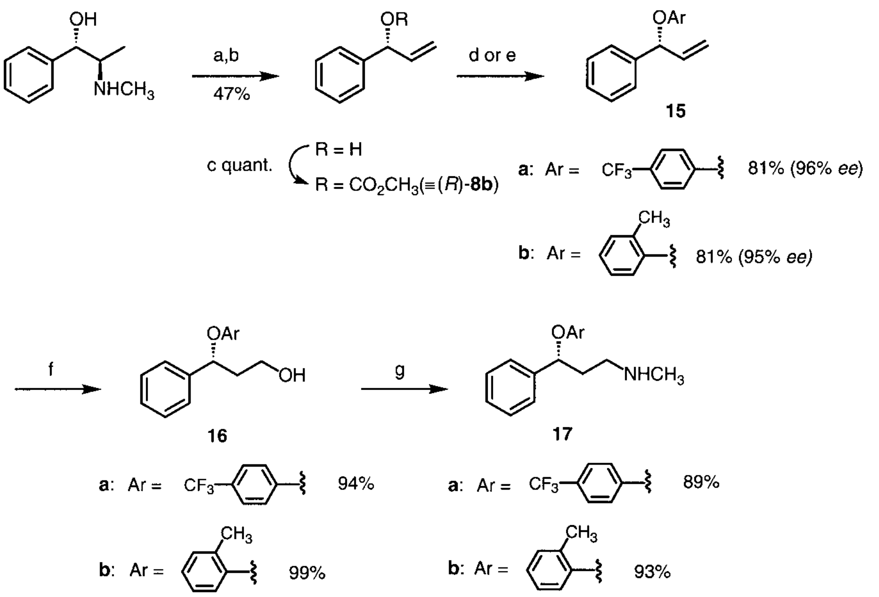

Scheme 1. Synthesis of antidepressants. a) CH_3I, K_2CO_3, CH_3OH, RT; b) LDA, THF, HMPA, −50 to 0 °C; c) n-C_4H_9Li, $ClCO_2CH_3$, THF, −78 to 0 °C; d) 1 mol% **7**, p-$CF_3C_6H_4OTMS$, 1 mol% TBAT, neat, 35 °C; e) 1 mol% **7**, o-$CH_3C_6H_4OTMS$, 5 mol% $(n\text{-}C_4H_9)_4NCl$, 10 mol% $(C_2H_5)_3N$, neat, 35 °C; f) 9-BBN-H, THF, 35 °C then KOH, H_2O_2, 0 °C; g) CH_3SO_2Cl, $(C_2H_5)_3N$, CH_2Cl_2, 0 °C then CH_3NH_2, CH_3OH, 70 °C. LDA = lithium diisopropylamide, HMPA = hexamethylphosphoramide, 9-BBN-H = 9-borabicyclo[3.3.1]nonane.

desilylating agent (tetrabutylammonium triphenyldifluorosilicate (TBAT) or tetrabutylammonium chloride (TBAC)) with 1 mol% of **7** under neat conditions effected the desired reaction. The reaction of the trimethylsilyl ether of p-trifluorocresol gave a 7:1 b/l ratio from which **15a** was isolated in 81% yield.

Standard hydroboration, oxidation, and substitution provided (−)-fluoxetine (**17**). Switching to the o-cresol system similarly gave a 6:1 b/l ratio from which **15b** was isolated in 81% yield. In both cases, excellent chirality transfer is observed, demonstrating the effectiveness of our catalyst for both carbon and heteroatom nucleophiles.

The ruthenium-catalyzed allylic alkylation differs from previous catalytic systems in several important respects. Like Pd, Mo, and W—but unlike Rh—regioselectivity is not highly dependent on the nature of the starting carbonate. Unlike Pd and Mo, but like Rh and W, substitution of the scalemic chiral substrate occurs with high net retention of configuration. Heteroatom nucleophiles which fail with Mo and W succeed with this system. Thus, this catalyst nicely complements the previously developed systems. Importantly, reactions proceed extremely well under mild conditions with 1 mol% of catalyst. The solvent-free conditions are commensurate with the ideals of green chemistry. The practicality of the methodology is illustrated by a novel synthesis of (R)-fluoxetine and (R)-tomoxetine starting from inexpensive ephedrine using a heretofore unknown elimination to generate the allyl alcohol of high enantiopurity.

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