Ruthenium-catalyzed stereospecific decarboxylative allylation of non-stabilized ketone enolates†

Erin C. Burger and Jon A. Tunge*

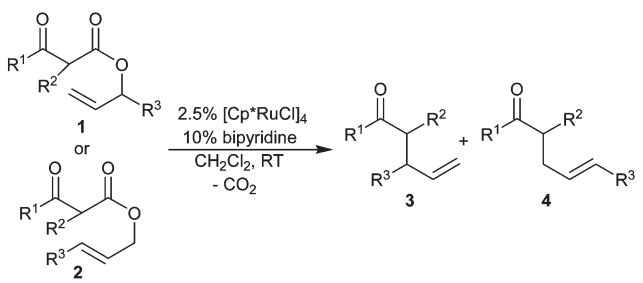
Received (in Bloomington, IN, USA) 7th March 2005, Accepted 7th April 2005
First published as an Advance Article on the web 21st April 2005
DOI: 10.1039/b503568f

The ruthenium-catalyzed stereospecific decarboxylative allylation of ketone enolates provides access to γ,δ-unsaturated ketones with good yields and enantioenrichments.

The ability to synthesize small molecules that are highly enantioenriched is an important goal in organic synthesis. Optically active γ,δ-unsaturated ketones are particularly attractive targets due to the complementary reactivity of the electrophilic carbonyl and the nucleophilic olefin. Moreover, these molecules can be further elaborated by diastereoselective additions in order to synthesize more complex targets as single enantiomers.[1] During the course of our studies[2] on a catalytic version of the decarboxylative Claisen (Carroll) rearrangement,[3,4] we disclosed the use of $[Cp^*RuCl]_4$ as a catalyst to provide γ,δ-unsaturated ketones (**3**) in high yields *via* the regioselective decarboxylative allylation of non-stabilized ketone enolates (Scheme 1).[2a] We now wish to report that our catalytic decarboxylative rearrangement is also highly stereospecific, allowing the synthesis of enantioenriched γ,δ-unsaturated ketones. Furthermore, we have identified the primary mechanism for racemization and used this knowledge to maximize the stereospecificity.

Stereospecific allylations of stabilized malonate enolates have been previously reported with ruthenium,[5] rhodium,[6] iridium,[7] and palladium.[8] Evans recently expanded the scope of Rh-catalyzed allylic alkylations to include the first examples of a stereospecific allylation of *non-stabilized* ketone enolates which proceeds *via* the *in situ* formation of copper enolates.[6c,d] This prompted us to examine the stereochemical fidelity of our ruthenium-catalyzed allylation of non-stabilized enolates.

To begin, model substrate (*S*)-**1a** (R^1 = Me; R^2 = H; R^3 = Ph), was prepared with high enantiopurity (95% ee) *via* enzymatic resolution of the corresponding allylic alcohol followed by esterification with diketene.[9] We were encouraged to find the product (**3a**) was produced with a 79% ee (83% cee)‡ upon treatment of **1a** with 2.5 mol% $[Cp^*RuCl]_4$ and 10 mol% bipyridine at room temperature in CH_2Cl_2. Interestingly, the regioselectivity of the decarboxylative rearrangement (**3**:**4** = 75:1) is much higher than that reported for the related ruthenium-catalyzed allylation of dimethyl malonate (12:1).[5] Furthermore, we have confirmed that the reaction occurs with net retention of configuration by hydrogenation of **3a** to produce (*R*)-(−)-4-phenyl-2-hexanone.[10] Thus, our allylation of a non-stabilized ketone enolate is stereochemically analogous to Trost's ruthenium-catalyzed allylation of stabilized malonate nucleophiles.[5] However, racemization was not observed in reactions of allylic carbonates with stabilized nucleophiles, indicating that our reaction may differ mechanistically.



Scheme 1 Decarboxylative allylation.

A variety of other allylic β-keto esters underwent decarboxylative rearrangement to give good yields of the corresponding unsaturated ketones (**3**) with good retention of stereochemistry (Table 1). While aryl substitution on the allyl fragment is required for a facile, high-yielding reaction, the reaction tolerates a variety of electron donating and withdrawing substituents on the phenyl ring. Furthermore, in contrast to results obtained for straight-chain β-keto esters (**2**), reaction times for branched β-keto esters (**1**) do not show a strong dependence on the electronic nature of the aryl substituent.[2a] For example, while an electron withdrawing *p*-NO_2 substituent does not have a large effect on the rate of reaction of branched β-keto ester **1e** (*vs.* **1a**), the rate of reaction of NO_2-substituted straight-chain β-keto ester **2e** is decreased *ca.* 20-fold relative to **2a**.

In addition to variation of the aryl group, a variety of enolates (**1f–1h**) are accessible through decarboxylation. The results of these studies indicate that *enolate generation is regiospecific*, with the regiochemistry determined solely by the position that carries the carboxylate group. It is particularly noteworthy that we are able to access the terminal enolate of benzyl acetone (from **1g**), which cannot be accomplished with standard base-induced enolate formation.[11]

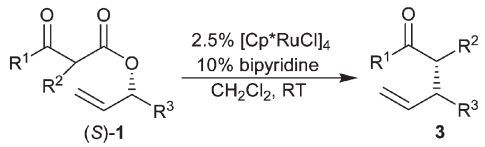
The effects of nitrogenous bidentate ligands other than bipyridine were also briefly explored. It was found that TMEDA (tetramethyethylenediamine) leads to decreased retention of stereochemistry for most substrates; the exception to this is **1a**, which produced **3a** with slightly elevated conservation of configuration using TMEDA as a ligand. Since there was no clear trend, the origin of these effects is not completely understood.

Having demonstrated that the rearrangement is enantiospecific, we turned our attention to identifying the mechanism(s) responsible for imperfect retention of configuration. Racemizations of

† Electronic supplementary information (ESI) available: experimental and characterization of new compounds. See http://www.rsc.org/suppdata/cc/b5/b503568f/

*tunge@ku.edu

Table 1 Reaction with various aryl substrates[a]



Substrate	R^1	R^2	R^3	Time	**3**:**4**[b]	cee[c] (%)	Yield (%)
1a	Me	H	Ph	1.5 h	75:1	83	86
1a	Me	H	Ph	4 h	—	87[d]	N/A
1b	Me	H	*p*-MeC_6H_4	2 h	101:1	87	81
1c	Me	H	*p*-$(MeO)C_6H_4$	15 min	19:1	93	83
1c	Me	H	*p*-$(MeO)C_6H_4$	—	>19:1	52[d]	N/A
1d	Me	H	*p*-ClC_6H_4	4 h	—	86	70
1d	Me	H	*p*-ClC_6H_4	30 min	89:1	94	56
1e	Me	H	*p*-$(NO_2)C_6H_4$	3 h	>19:1	98	49
1e	Me	H	*p*-$(NO_2)C_6H_4$	2 h	>19:1	45[d]	N/A
1f	Me	Me	Ph	2 h	59:1	93[e]	76
1g	Bn	H	Ph	3 h	20:1	72	71
1g	Bn	H	Ph	1 h	—	79	49
1h	*i*-Pr	H	Ph	3 h	38:1	58	68

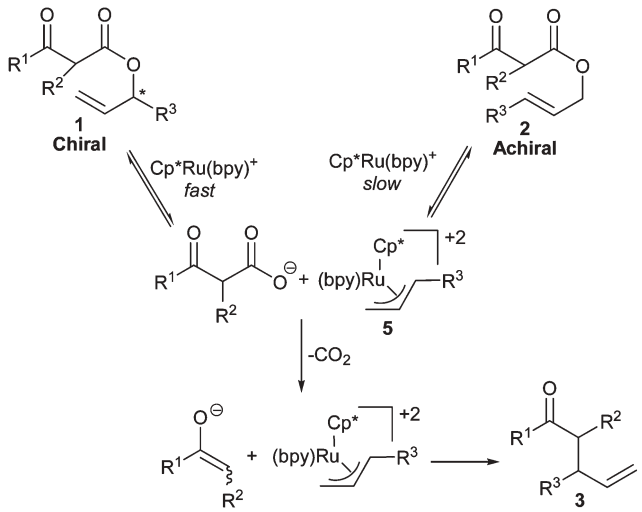
[a] Reactions run at 0.1 M in CH_2Cl_2 at room temperature with 2.5 mol% $[Cp^*RuCl]_4$ and 10 mol% bipyridine. [b] Determined by GC or ^1H NMR spectroscopy of the crude reaction mixture; > 19:1 indicates that the minor regioisomer was not observed by NMR spectroscopy. [c] Determined on a Diacel Chiralpak AD or OD-H HPLC column. [d] With 10 mol% TMEDA ligand. [e] cee of major diastereomer; dr = 1:1.5.

related palladium π-allyl complexes have been shown to occur by π–σ–π interconversion of the enantiotopic allyl faces and/or by a bimetallic mechanism involving degenerate substitution of a palladium π-allyl by Pd^0.[12] It has also been suggested,[8a] and later refuted,[12] that nonselective attack of the acetate leaving group on the π-allyl is responsible for reduced stereospecificity in alkylations of allylic acetates. While much less is known about the mechanism of racemization of ruthenium π-allyl complexes, Trost has shown that racemization by π–σ–π allyl interconversion is slow at ambient temperature.[5]

To begin, a brief survey of reaction conditions demonstrated that the concentration of the reaction mixture impacts the stereospecificity of decarboxylative allylation. For example, when various concentrations of **1c** (0.32 M to 0.04 M) were allowed to undergo catalytic rearrangement with 2.5 mol% $[Cp^*RuCl]_4$ and 10 mol% bpy, it was found that as the concentration of **1c** decreased, the retention of stereochemistry in product **3c** increased from 86% to 94% cee. While this difference is significant, the magnitude is much smaller than would be predicted based on a bimetallic racemization mechanism;[12] an 8-fold increase in catalyst concentration would be expected to increase the rate of racemization by a factor of 64.

Another important observation was that enantioenrichment of **3** is dependent on conversion. For example, the ee of **3a**, produced from the rearrangement of **1a** (93.5% ee), gradually decreased from 93% to 76% over a 20 minute reaction period.

Further investigation of the course of the reaction *via* ^1H NMR spectroscopy proved to be particularly revealing. After five minutes of catalysis (*ca.* 50% conv.) under standard reaction conditions we observed partial isomerization of the branched, chiral β-keto ester **1c** to linear, achiral β-keto ester **2c** (4:1 ratio of **1c**:**2c**). The isomerization of **1** to **2** was subsequently observed for all substrates (Scheme 2). This isomerization can lead to loss of stereochemistry *via* two related routes: A) the racemization of **1** *via* equilibration between **1** and **2** and B) the production of racemic **3** from the decarboxylative rearrangement of achiral substrate **2**. In



Scheme 2 Mechanism of racemization.

fact, we have evidence that both of these routes contribute to production of racemic **3**.

In the case of **1c**, degradation of enantiopurity of the starting material was directly observed. It was found that the ee of **1c** decreased from 94% to 78% after five minutes of catalysis (*ca.* 50% conv.). Thus, the racemization of **1** contributes to imperfect retention of stereochemistry in product **3**. While ionization to π-allyl complex **5** followed by π–σ–π isomerization could explain this result, we do not believe that this is the case for the following reasons: 1) Trost has shown that π–σ–π isomerization in related ruthenium-π-allyl complexes is slow and 2) we directly observed substantial quantities (20%) of isomerization product **2c** in the reaction mixture, implicating equilibration of **1** and **2** as a simple mechanism for racemization of **1** (mechanism A).

A further observation from the ^1H NMR spectroscopic analysis is that branched isomer **1** undergoes rearrangement to **3** faster than

the corresponding linear isomer **2**. This can be in part explained by a more facile pre-coordination of the Ru catalyst to the monosubstituted allyl fragment found in **1** compared to the conjugated, disubstituted allyl fragment present in **2**. Based on this result, we surmised that the difference in reactivity between substrates **1** and **2** could be exploited in order to generate products with increased retention of stereochemistry by avoiding the production of racemic **3** through mechanism B. For example, when substrate **1d** (96% ee) was allowed to react for 4 hours in order to maximize conversion to product, **3d** was isolated in 70% yield and 83% ee (86% cee, Table 1). However, ^{1}H NMR spectroscopy indicated that after 30 minutes only linear, achiral β-keto ester **2** remained. Thus, allowing the reaction to proceed for only 30 minutes allowed us to isolate **3d** in 90% ee (94% cee), albeit in lower chemical yield (56%).

This strategy was useful for improving cee's of substrates for which isomeric forms **1** and **2** have substantially different rearrangement kinetics. Substrates **1e** and **2e** provide the most striking example of the differential reactivity between the two isomers of starting material. In this case the reaction of **2e** is extremely slow (*vide supra*) under the conditions of catalysis, virtually eliminating the reaction pathway leading from **2** to racemic product. Presumably the difference in rates is due to the presence of the strongly withdrawing nitro group. Bruneau, *et al.* have suggested that, prior to oxidative addition and π-allyl formation, Ru pre-coordinates to the olefin.[13] Backbonding into the π* orbital of the alkene is expected to be greatest for electron deficient aryl substituted alkenes (**2**). This in turn decreases the nucleophilicity of Ru, which will raise the barrier for oxidative addition to form the reactive π-allyl ruthenium species (**5**). Thus, with electron withdrawing aryl groups, **2** is essentially unreactive, preventing the formation of racemic **3**. However, with electron donating aryl groups (*p*-OMe) the barrier for racemization is low enough that we have observed the partial racemization of **1c**.

The addition of an α-methyl group also leads to a large disparity between the reaction rates of **1f** and isomeric **2f**, allowing the isolation of **3f** in a 90% ee from 97% ee starting material (93% cee). This is compared to **3a** (non-methylated), which was isolated in a 79% ee from 95% ee starting material (83% cee). Clearly, understanding and utilizing the differing reaction rates of isomeric allyl β-keto esters is necessary in order to maximize the stereospecificity of decarboxylative allylations.

In summary, we have shown that the decarboxylative allylation of ketone enolates using a [Cp*RuCl]$_4$/bipyridine catalyst proceeds in a stereospecific manner. Furthermore, imperfect stereospecificity has been attributed to a ruthenium-catalyzed isomerization of starting material through reversible formation of π-allyl ruthenium intermediates. This mechanistic insight allowed us to develop a highly stereospecific decarboxylative allylation of non-stabilized ketone enolates.

Erin C. Burger and Jon A. Tunge*
Department of Chemistry, University of Kansas, Lawrence, Kansas. E-mail: tunge@ku.edu

Notes and references

‡ Conservation of enantiomeric excess (cee) = [product ee/reactant ee] × 100.

1 A. M. M. Castro, *Chem. Rev.*, 2004, **104**, 2939.
2 (*a*) E. Burger and J. Tunge, *Org. Lett.*, 2004, **6**, 2603; (*b*) E. Burger and J. Tunge, *Org. Lett.*, 2004, **6**, 4113; (*c*) E. Burger and J. Tunge, *Eur. J. Org. Chem.*, 2005, DOI: 10.1002/ejoc.200400865.
3 M. Carroll, *J. Chem. Soc.*, 1940, 704.
4 (*a*) T. Tsuda, Y. Chujo, S.-I. Nishi, K. Tawara and T. Saegusa, *J. Am. Chem. Soc.*, 1980, **102**, 6381–6384; (*b*) I. Shimizu, T. Yamada and J. Tsuji, *Tetrahedron Lett.*, 1980, **21**, 3199–3202.
5 B. Trost, P. Fraisse and Z. Ball, *Angew. Chem. Int. Ed.*, 2002, **41**, 1059.
6 (*a*) P. A. Evans and J. Nelson, *J. Am. Chem. Soc.*, 1998, **120**, 5581; (*b*) P. A. Evans and L. Kennedy, *Org. Lett.*, 2000, **2**, 2213; (*c*) P. A. Evans and D. Leahy, *J. Am. Chem. Soc.*, 2003, **125**, 8974; (*d*) P. A. Evans and M. Lawler, *J. Am. Chem. Soc.*, 2004, **126**, 8642.
7 (*a*) B. Bartels and G. Helmchen, *Chem. Commun.*, 1999, 741.
8 (*a*) B. Trost and T. Verhoeven, *J. Am. Chem. Soc.*, 1980, **102**, 4730; (*b*) T. Hayashi, T. Hagihara, M. Konishi and M. Kumada, *J. Am. Chem. Soc.*, 1983, **105**, 7767; (*c*) T. Konno, K. Nagata, T. Ishihara and H. Yamanaka, *J. Org. Chem.*, 2002, **67**, 1768.
9 (*a*) K. Burgess and L. Jennings, *J. Am. Chem. Soc.*, 1990, **112**, 7434; (*b*) K. Burgess and L. Jennings, *J. Am. Chem. Soc.*, 1991, **113**, 6129.
10 K. Soai, S. Yokoyama, T. Hayasaka and K. Ebihara, *J. Org. Chem.*, 1988, **53**, 4148.
11 E. J. Corey and A. W. Gross, *Tetrahedron Lett.*, 1984, **25**, 495.
12 P. B. Mackenzie, J. Whelan and B. Bosnich, *J. Am. Chem. Soc.*, 1985, **107**, 2046.
13 M. Mbaye, B. Demerseman, J. Renaud, L. Toupet and C. Bruneau, *Angew. Chem. Int. Ed.*, 2003, **42**, 5066.