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Ruthenium-Catalyzed Decarboxylative Insertion of Electrophiles

Chao Wang and Jon A. Tunge*

Department of Chemistry, University of Kansas, Lawrence, Kansas 66045

tunge@ku.edu

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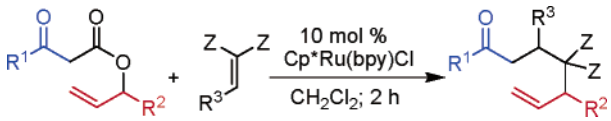
ABSTRACT

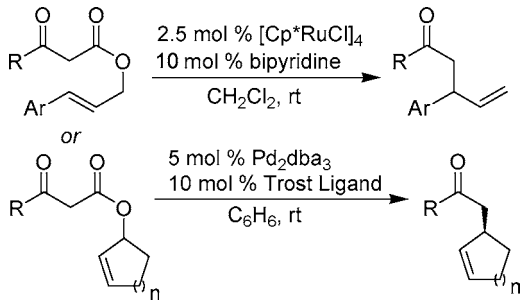


A ruthenium complex, Cp*Ru(bipyridyl)Cl, has been developed as a catalyst for the first regioselective tandem Michael addition–allylic alkylation of activated Michael acceptors. The net transformation is the decarboxylative insertion of Michael acceptors into allyl β-ketoesters.

The desire to rapidly generate complex molecules has driven the search for new catalytic processes that effect multiple transformations in one pot.[1] Notable recent examples include tandem cyclization−arylation,[2] allylic alkylation/Pauson−Khand,[3] and olefin metathesis−hydrogenation.[4] Each of these examples relies on the ability of a transition metal to catalyze two distinct sequential transformations. In contrast, a bifunctional catalyst that can simultaneously activate two components of a reaction mixture toward reaction with a third should facilitate multiple concurrent bond-forming reactions.

In previous work on the decarboxylative rearrangement of allyl β-ketoesters (Carroll rearrangement, Scheme 1), we

Scheme 1. Decarboxylative Allylation



and others have shown that transition metals behave as bifunctional catalysts;[5,6] they activate the electrophilic allyl fragment and catalyze the decarboxylative formation of enolate nucleophiles.[7]

At the time of our initial investigation, the asymmetric allylic alkylation (AAA) reaction was largely restricted to stabilized carbanionic nucleophiles ($pK_a < 18$).[8] Thus, we investigated the ability of different transition metals to catalyze the decarboxylative allylation of nonstabilized ketone enolates and found that Cp*Ru(bpy)Cl (bpy = 2,2′-bipyridyl) and various Pd^0 sources serve as effective catalysts.[5] In the course of these investigations, crossover experiments were performed to clarify the mechanism of these interesting transformations. When two equally reactive allyl β-ketoesters were allowed to react in the presence of 2.5 mol % $[Cp^*RuCl]_4$ and 10 mol % bipyridine (bpy), a statistical mixture of all four possible products was observed (Scheme 2). The case was similar when $Pd(PPh_3)_4$ was employed as a catalyst.

The crossover experiments suggest that allyl β-ketoesters are sources of freely diffusing enolates and allylic cations.

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(2) Lira, R.; Wolfe, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 13906−13907.
(3) Evans, P. A.; Robinson, J. E. *J. Am. Chem. Soc.* **2001**, *123*, 4609−4610.
(4) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312−11313.
(5) (a) Burger, E. C.; Tunge, J. A. *Org. Lett.* **2004**, *6*, 2603−2605. (b) Burger, E. C.; Tunge, J. A. *Org. Lett.* **2004**, *6*, 4113−4115. (c) Burger, E. C.; Tunge, J. A. *Eur. J. Org. Chem.* **2005**, 1715−1726.
(6) (a) Tsuda, T.; Chujo, Y.; Nishi, S.-I.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6381−6384. (b) Shimizu, I.; Yamada, T.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 3199−3202.
(7) (a) Lou, S.; Westbrook, J. A.; Schaus, S. E. *J. Am. Chem. Soc.* **2004**, *126*, 11440−11441. (b) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044−15045. (c) Lalic, G.; Aloise, A. D.; Shair, M. D. *J. Am. Chem. Soc.* **2003**, *125*, 2852−2853.
(8) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395−422.

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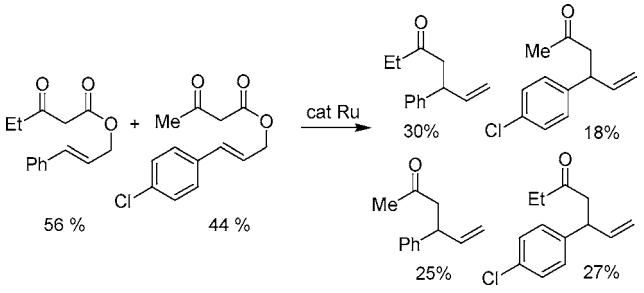
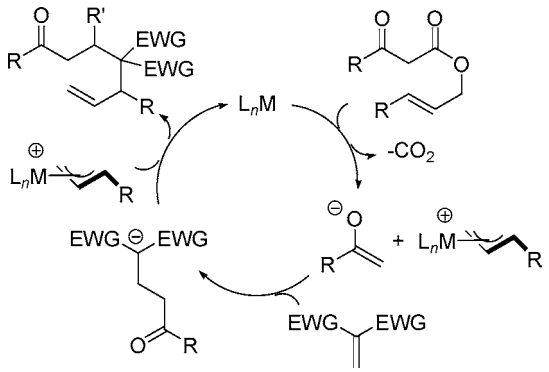
Scheme 2. Crossover Experiment



While this is a clear oversimplification, we became curious whether such reactive intermediates could be intercepted by an appropriate reactant. The enolates generated by palladium-catalyzed decarboxylation have been intramolecularly trapped by aldehydes and Michael acceptors.[9] Recent focus has been on extending this reactivity toward intermolecular interception of the enolate.[7a] Toward this end, Yamamoto reported that methylene malonitriles react with allyl acetoacetate in the presence of catalytic Pd(0) to give the product of β-acetonation and α-allylation.[10]

With this precedent, we decided to investigate the tandem Michael addition−allylation of pronucleophiles under our conditions for ruthenium-catalyzed decarboxylative allylation.[5a] We envisioned that enolate addition to activated Michael acceptors ($RCH{=}CZ_2$) would produce stabilized enolates, which are well-known nucleophiles for metal-catalyzed allylic substitution (Scheme 3).[8] Thus, Michael acceptors are

Scheme 3. Catalytic Cycle



ideally set up to undergo tandem enolate addition and allylation. Furthermore, the vast literature on metal-catalyzed allylic alkylations suggests that the regiochemistry of the allylation can be controlled by the appropriate choice of the transition metal catalyst.[5,11]

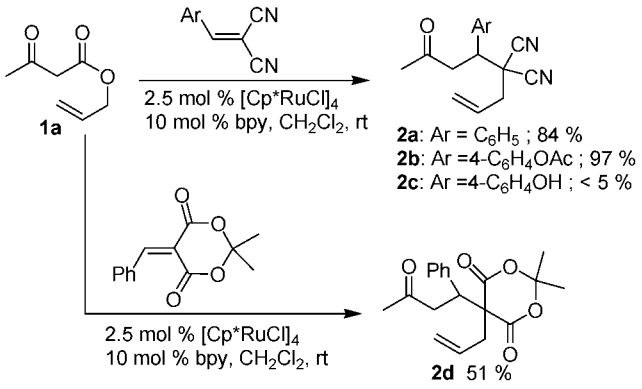
(9) (a) Nokami, J.; Mandai, T.; Watanabe, H.; Ohyama, H.; Tsuji, J. *J. Am. Chem. Soc.* **1989**, *111*, 4126−4127. (b) Nokami, J.; Watanabe, H.; Mandai, T.; Kawada, M.; Tsuji, J. *Tetrahedron Lett.* **1989**, *30*, 4829−4832.

(10) Shim, J.-G.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 8470−8474.

(11) Trost, B. M.; Fraisse, P. L.; Ball, Z. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1059−1061.

We initiated our study by investigating the range of Michael acceptors that are compatible with the tandem Michael addition−allylation under the conditions previously developed for catalytic Carroll-type rearrangement of allyl β-ketoesters.[5] The most successful reactions were those with olefins containing two electron-withdrawing groups. Thus, benzylidene malononitrile (**3a**, Ar = Ph, $E = -9.42$)[12] provided a high yield of the tandem Michael addition−allylation product **2a** in only 2 h at ambient temperature (Scheme 4). The electronics of the malononitrile are crucial

Scheme 4. Decarboxylative Olefin Insertion



to the success of the decarboxylative insertion.[13] This is illustrated by the <5% yield of Michael addition−allylation product **2c** when *p*-hydroxybenzylidene malononitrile is employed as the electrophile.[14] In this case, *p*-hydroxybenzylidene malononitrile is not sufficiently electrophilic ($E \sim -10.8$)[12] to efficiently trap the enolate;[15] acylation of the hydroxyl group is sufficient to restore activity. The Knoevenagel adduct of benzaldehyde and Meldrum's acid is also an effective Michael acceptor,[16] showing that activated diesters are also viable reaction partners.

Next, we turned our attention to developing the first regioselective tandem Michael addition−allylation. It was gratifying to find that treatment of **1f** (R^1 = Me, R^2 = Ph) with benzylidene malononitrile, 2.5 mol % $[Cp^*RuCl]_4$, and 10 mol % bipyridine at room temperature in CH_2Cl_2 produced **2f** in high yield (89%) (Scheme 5). The analogous palladium-catalyzed reaction produced the opposite regioisomer **4f** in 80% yield. The regioselectivities for ruthenium

Scheme 5. Catalyst-Dependent Selectivity

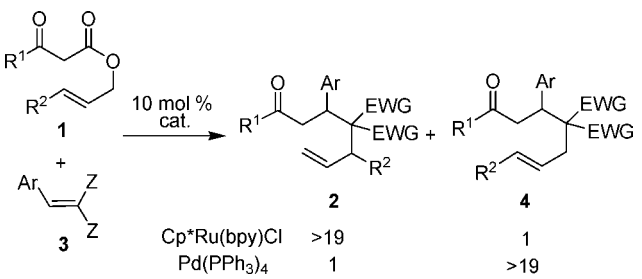
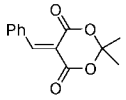
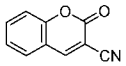
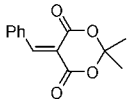


Table 1. Yields of Tandem Michael Addition−Allylation Using Allyl β-Ketoesters $R^1COCH_2CO_2CH(R^3)CHCHR^2$ [a,b]

R^1	R^2	R^3	Michael acceptor	prod	time (h)	% yield (dr)[a]
Me	H	H	**3a**	**2a**	2	84
Me	H	H	**3b**	**2b**	5	97
Me	H	H		**2d**	1.5	51
Me	H	H		**2e**	11	45 (12:1)
Me	Ph	H	**3a**	**2f**	12	89 (1.9:1)
Me	H	Ph	**3a**	**2f**	6	85 (3.5:1)
Bn	H	H	**3a**	**2g**	4.5	87
Ph	H	H	**3a**	**2h**	5.5	64
Et	Ph	H	**3a**	**2i**	22	93 (1.8:1)
Me	H	*p*-C_6H_4OMe	**3a**	**2j**	18	62 (1.6:1)
Me	H	*p*-C_6H_4Cl	**3a**	**2k**	19	62 (1.8:1)
Me	Ph	H	**3b**	**2l**	48	92 (2.7:1)
Me	H	Ph	**3b**	**2l**	16	76 (4.5:1)
Me	Ph	H	**3a**	**4f**[c]	13	80
Et	Ph	H	**3a**	**4i**[c]	17	88
Me				**4m**[c]	12	65 (5.5:1)

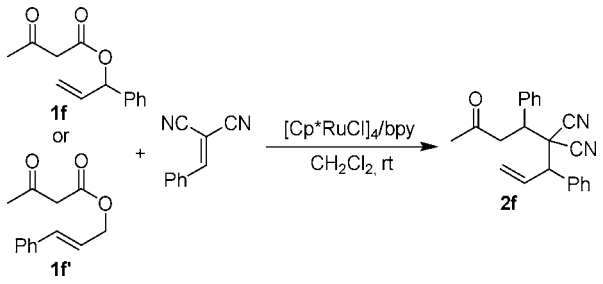
[a] Unless otherwise stated, the reactions were carried out with 1 (0.2 M), Michael acceptor (0.2 M), $[Cp^*RuCl]_4$ (0.005 M), and bpy (0.02 M) in CH_2Cl_2 at room temperature. [b] Isolated after column chromatography. [c] Using 10 mol % $Pd(PPh_3)_4$.

and palladium catalysts are consistent with those observed for other allylation reactions.[8,11]

A variety of allyl β-ketoesters undergo smooth decarboxylative coupling with Michael acceptors (Table 1). Variation of the R_1 group shows that the reaction is typified by regiospecific formation of enolates (Scheme 5). It is noteworthy that equilibration of the kinetic enolate does not occur even when R^1 is benzyl and there is a large thermodynamic driving force favoring the formation of the stabilized enolate. In fact, previous attempts to generate the terminal enolate of phenylacetone by deprotonation have failed.[17]

As expected for a reaction involving π-allyl ruthenium intermediates, the regioisomeric allyl β-ketoesters **1f** and **1f′** give the same product (**2f**, Scheme 6); however, the less

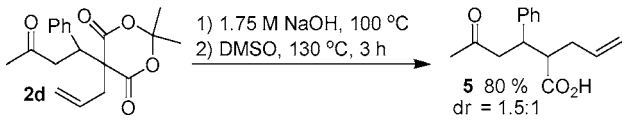
Scheme 6. Regioselective Allylation



substituted olefinic reactant (**1f**) provides product more rapidly. Consistent with this trend, the unsubstituted allyl partners generally react most quickly. This implies that coordination of the alkene to ruthenium may be important in the rate-limiting step.

Finally, to illustrate the utility of the benzylidene Meldrum electrophiles, we performed a simple hydrolysis and decarboxylation of **2d** (Scheme 7). The resulting γ,δ-unsaturated

Scheme 7. Hydrolysis of Diester **2d**



acids such as **5** are particularly useful substrates for halolactonizations.[18]

In conclusion, we have developed a regioselective, catalytic coupling of enolates, Michael acceptors, and allyl electrophiles. The tandem Michael addition−allylation is made possible by the decarboxylative activation of allyl β-ketoesters to produce enolates and π-allylmetal electrophiles. We are currently exploring similar reactions that exploit our ability to regiospecifically generate enolates from β-keto esters at room temperature under base-free conditions.

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Supporting Information Available: Experimental procedures and spectroscopic data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For electrophilicity parameters of benzylidene malonitriles, see: Lemek, T.; Mayr, H. *J. Org. Chem.* **2003**, *68*, 6880−6886.

(13) We have not investigated alkyl-substituted malononitrile derivatives due to their instability under the reaction conditions[10]

(14) The only products observed are those of the Carroll-type rearrangement.[5a]

(15) Electrophilicity of the π-allyl ruthenium complex must be similar to the π-allyl palladium complex (η^3-PhCHCHCH)Pd[P(OPh)$_3$]$_2$ (−10.33). Kuhn, O.; Mayr, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 343−346.

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(18) Mellegaard, S. R.; Tunge, J. A. *J. Org. Chem.* **2004**, *69*, 8979−8981.