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COMMUNICATION

Synthesis of α,β-unsaturated γ-amino esters with a quaternary center by ruthenium-catalyzed codimerization of *N*-acetyl α-arylenamines and acrylates†

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Ruthenium-catalyzed highly selective codimerization of *N*-acetyl α-arylenamines with ethyl acrylates is reported. This codimerization reaction provides a new efficient method for the synthesis of α,β-unsaturated γ-amino esters with a quaternary center.

α,β-Unsaturated γ-amino esters are very useful intermediates and building blocks in organic synthesis.[1] They can be found in various bioactive natural products and drug molecules, such as miraziridine A, a novel cysteine protease inhibitor from the marine sponge *Theonella* aff. *mirabilis*,[2] and AG7088, a rhinovirus protease inhibitor for treatment of the common cold [3] (Fig. 1). More importantly, α,β-unsaturated γ-amino esters can serve as precursors for the preparation of γ-amino acids, which are key ingredients in pharmaceuticals.[4] α,β-Unsaturated γ-amino esters are usually prepared from *N*-protected α-amino aldehydes by Witting-type olefination reactions.[5] Direct catalytic syntheses of α,β-unsaturated γ-amino esters are very limited. The reported catalytic methods include the palladium-catalyzed rearrangement of α-sulfonimidoyl β,γ-unsaturated esters,[6] the palladium-catalyzed insertion of α-diazoesters into vinyl halides and trapping with amines,[7] rhodium- and palladium-catalyzed ring opening of vinyl epoxides with amines and azide,[8] and Lewis acid-catalyzed N–H insertions of methyl styryldiazoacetate with aniline.[9] However, the efficiencies of these methodologies, especially in the preparation of the α,β-unsaturated γ-amino esters with a quaternary center, are unsatisfied. Therefore, the development of highly efficient and atom-economic catalytic methods for the synthesis of α,β-unsaturated γ-amino esters is highly desired.

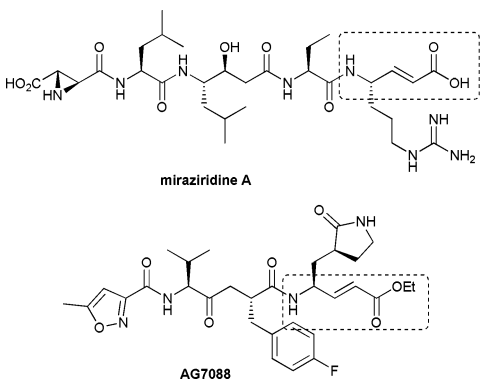
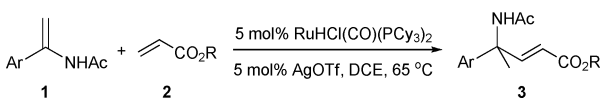


Fig. 1 Bioactive molecules containing the α,β-unsaturated γ-amino acid/ester moiety.

Transition metal-catalyzed selective codimerization of two different alkenes, for example hydrovinylation, is a very important and highly atom-efficient olefin-forming reaction, and has been the subject of extensive study.[10] Recently, we studied codimerizations of α-substituted vinylarenes with ethylene (hydrovinylation) and obtained olefin products with a quaternary center in high yields and high chemoselectivities[11] This result encouraged us to investigate the codimerization of *N*-acetylenamines with functionalized alkenes to generate polyfunctionalized alkenes. In this communication, we report the codimerization of *N*-acetyl α-arylenamines with acrylates catalyzed by a ruthenium complex $RuHCl(CO)(PCy_3)_2$, producing α,β-unsaturated γ-amino esters with a quaternary center in high yields (Scheme 1).[12]



Scheme 1 The codimerization of *N*-acetyl α-arylenamines with acrylates.

The codimerization reaction was initially performed under the standard conditions for the hydrovinylation of *N*-acetylenamines.[11d] The reaction of *N*-(1-phenylvinyl)acetamide (**1a**) with 2.0 equivalents of ethyl acrylate (**2a**) in the presence of 5 mol% of catalyst $RuHCl(CO)(PCy_3)_2$ and 5 mol% of additive AgOTf in DCE at 65 °C produced α,β-unsaturated γ-amino ester (*E*)-**3a** in 85% yield accompanied by a small amount (~5%) of by-product formed from the dimerization of **1a** (Table 1, entry 1). On increasing the amount of ethyl acrylate (**2a**) from 2.0 to 5.0 equivalents, the reaction became faster (reaction time changed from 40 h to 3.5 h) and the yield of **3a** increased to 96% (entry 2). However, changing the ruthenium catalyst to $RuH_2(CO)(PPh_3)_3$ or

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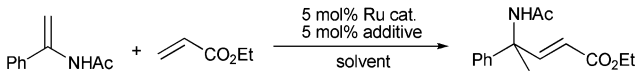
Table 1 Reaction conditions optimization for the codimerization of **1a** and **2a**[a]



1a 2a 3a

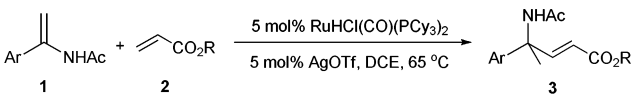
Entry	Catalyst	Additive	Solvent	Temp./°C	Time/h	Conv. (%)	Yield (%)[b]
1[c]	$RuHCl(CO)(PCy_3)_2$	AgOTf	DCE	65	40	> 97	85
2	$RuHCl(CO)(PCy_3)_2$	AgOTf	DCE	65	3.5	100	96
3	$RuH_2(CO)(PPh_3)_3$	None	DCE	65	20	27	*None*
4	$RuH_2(CO)(PPh_3)_3$	None	Toluene	140	20	41	*None*
5[d]	$[Ru(p\text{-cymene})Cl_2]_2/PPh_3$	$NaHCO_2$	Toluene	140	20	25	*None*
6	$RuHCl(CO)(PPh_3)_3$	AgOTf	DCE	65	20	13	*None*
7	$RuHCl(CO)(PCy_3)_2$	AgOTf	DCE	45	19	100	90
8	$RuHCl(CO)(PCy_3)_2$	AgOTf	DCE	25	72	92	86
9	$RuHCl(CO)(PCy_3)_2$	AgOTf	Toluene	65	20	76	33
10	$RuHCl(CO)(PCy_3)_2$	AgOTf	DMF	65	20	8	0
11	$RuHCl(CO)(PCy_3)_2$	AgOTf	Dioxane	65	20	51	47
12	$RuHCl(CO)(PCy_3)_2$	$AgBF_4$	DCE	65	20	100	86
13	$RuHCl(CO)(PCy_3)_2$	$AgPF_6$	DCE	65	20	63	60
14	$RuHCl(CO)(PCy_3)_2$	$AgSbF_6$	DCE	65	20	100	91
15	$RuHCl(CO)(PCy_3)_2$	$NaBAr_F$	DCE	65	20	82	77
16[e]	$RuHCl(CO)(PCy_3)_2$	AgOTf	DCE	65	40	86	80

[a] Reaction conditions: 0.01 mmol of [Ru] catalyst, 0.01 mmol of additive, 0.2 mmol of **1a**, 1.0 mmol of **2a** (5 eq.), 3 mL of solvent, 20 h. [b] Isolated yield. [c] 2 equivalents of **2a**. [d] 15 mol% of PPh_3, 30 mol% of $NaHCO_2$. [e] 2 mol% catalyst.

$[Ru(p\text{-cymene})Cl_2]_2/PPh_3$, which are efficient for the addition of olefinic C–H bonds of α,β-unsaturated ketones/esters to olefins,[12a–d] led only to dimerization of **1a**. The reaction temperature strongly influenced reaction rate. Lowering the reaction temperature to 45 °C and 25 °C decreased the reaction rate and gave lower yields (entries 7 and 8 *vs.* entry 2). Solvent screening experiments revealed that dichloroethane (DCE) was the best reaction medium, and coordinating solvents such as *N*,*N*-dimethylformamide (DMF) afforded no desired product. Trifluoromethanesulfonic acid anion (OTf^-) was demonstrated to be the counteranion of choice for the catalyst, albeit that the codimerization of **1a** and **2a** proceeded well with other counteranions such as BF_4^-, PF_6^-, SbF_6^-, and BAr_F^- (entries 12–15). The reaction can be carried out at 2 mol% of catalyst load, yielding codimerization product **3a** in 80% yield with 86% conversion (entry 16).

A variety of *N*-acetyl α-arylenamines **1** was studied under the optimal reaction conditions. The electronic property of the α-arylenamine substrate has a strong effect on the reaction rate and the yield of α,β-unsaturated γ-amino ester product. Substrates containing an electron-donating group at the *para*- or *meta*-position of the phenyl ring of the α-arylenamine showed high reaction rates and high yields (Table 2, entries 2, 3 and 8). Substrates having an electron-withdrawing group exhibited slow reaction rates, however the yields of the codimerizations are still high (entries 4–7). The reaction was also sensitive to the steric effect of the substituents on the substrates. *ortho*-Substitution on the ring of the α-arylenamine substrate led to a slower reaction and a lower yield, especially *N*-acetyl-α-(2-methylphenyl)enamine gave only 22% yield and 53% conversion (entry 9). Substrate α-(2-naphthyl)enamine also gave the desired codimerization product in high yield. The R group of the acrylate has little impact on the reaction except in the case of the very bulky ^{t}Bu (**2c**), which resulted in a low reaction rate, although the yield of the reaction was kept at 88%.

Table 2 Codimerization of *N*-acetyl α-arylenamines with acrylates catalyzed by $RuHCl(CO)(PCy_3)_2$[a]

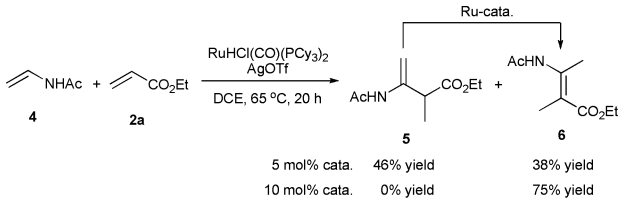


1 2 3

Entry	Ar	R	Product	Time/h	Conv. (%)	Yield (%)[b]
1	C_6H_5	Et	**3a**	3.5	100	96
2	$4\text{-}MeC_6H_4$	Et	**3b**	3.5	100	91
3	$4\text{-}MeOC_6H_4$	Et	**3c**	2.5	100	90
4	$4\text{-}FC_6H_4$	Et	**3d**	20	100	85
5	$4\text{-}ClC_6H_4$	Et	**3e**	12	100	90
6	$4\text{-}BrC_6H_4$	Et	**3f**	12	100	93
7	$3\text{-}BrC_6H_4$	Et	**3g**	12	100	87
8	$3\text{-}MeC_6H_4$	Et	**3h**	4	100	88
9	$2\text{-}MeC_6H_4$	Et	**3i**	20	53	22
10	$2\text{-}MeOC_6H_4$	Et	**3j**	14	100	83
11	2-Naphthyl	Et	**3k**	8	100	95
12	C_6H_5	Me	**3l**	3	100	92
13	C_6H_5	^{t}Bu	**3m**	20	95	88

[a] The reaction conditions were the same as those in Table 1, entry 2. For details of operation and analysis, see ESI. [b] Isolated yield.

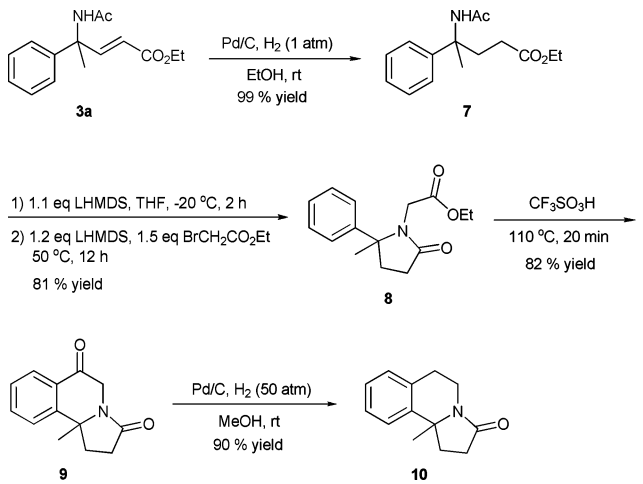
The codimerization reaction of *N*-vinylacetamide (**4**) with ethyl acrylate (**2a**) was also studied (Scheme 2). When the reaction was performed with 5 mol% catalyst codimerization products **5** and **6** were obtained in 46% and 38% yield, respectively. By adding another 5 mol% catalyst to the reaction mixture, compound **5** was converted to compound **6**. If 10 mol% catalyst was directly used in the beginning, the reaction gave only compound **6**. These results showed that the reaction may produce compound **5** first, which is isomerized to the more stable compound **6** in the presence of catalyst $RuHCl(CO)(PCy_3)_2/AgOTf$. The reaction of *N*-vinylacetamide with ethyl acrylate produced β,γ-unsaturated β-amino ester **5**, instead of the expected α,β-unsaturated γ-amino



Scheme 2 Codimerization of *N*-vinylacetamide (**4**) and ethyl acrylate (**2a**).

ester, indicating that the reaction might proceed *via* a different mechanism.[11d]

To demonstrate the utility of the codimerization products, α,β-unsaturated γ-amino esters, as key intermediates in organic synthesis, we converted **3a** to tricyclic compound **10**, which is the structural motif in natural products of the *Erythrina* alkaloids group.[13] The α,β-unsaturated γ-amino ester **3a** was hydrogenated over Pd/C catalyst to give saturated γ-amino ester **7** in quantitative yield. Treatment of the γ-amino ester **7** with LHMDS, followed by reaction with ethyl 2-bromoacetate, gave the substituted 2-pyrrolidinone **8** in 81% yield. Cyclization of **8** under acidic conditions, followed by a reduction with Pd/C under hydrogen, afforded the tricyclic compound **10** (Scheme 3). This study provided a new efficient approach to the synthesis of pyrroloisoquinoline-type tricyclic compounds with a quaternary center.



Scheme 3 Synthesis of tricyclic compound **10**.

In conclusion, we have developed an efficient ruthenium-catalyzed codimerization of *N*-acetyl α-arylenamines with acrylates. The new reaction provides convenient access to α,β-unsaturated γ-amino esters with a quaternary center. Further studies on this reaction, especially in searching for efficient chiral ligands to accomplish chiral induction, are in progress in our laboratory.

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Notes and references

1 For reviews of the preparation and synthetic applications of α,β-unsaturated γ-amino esters, see: (*a*) M. T. Reetz, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1531; (*b*) M. T. Reetz, *Chem. Rev.*, 1999, **99**, 1121; (*c*) D. Gryko, J. Chalko and J. Jurczak, *Chirality*, 2003, **15**, 514.
2 Y. Nakao, M. Fujita, K. Warabi, S. Matsunaga and N. Fusetani, *J. Am. Chem. Soc.*, 2000, **122**, 10462.
3 (*a*) P. S. Dragovich, T. J. Prins, R. Zhou, S. E. Webber, J. T. Marakovits, S. A. Fuhrman, A. K. Patick, D. A. Matthews, C. A. Lee, C. E. Ford, B. J. Burke, P. A. Rejto, T. F. Hendrickson, T. Tuntland, E. L. Brown, J. W. Meador III, R. A. Ferre, J. E. V. Harr, M. B. Kosa and S. T. Worland, *J. Med. Chem.*, 1999, **42**, 1213; (*b*) Q. Tian, N. K. Nayyar, S. Babu, L. Chen, J. Tao, S. Lee, A. Tibbetts, T. Moran, J. Liou, M. Guo and T. P. Kennedy, *Tetrahedron Lett.*, 2001, **42**, 6807.
4 F. Bouillère, S. Thétiot-Laurent, C. Kouklovsky and V. Alezra, *Amino Acids*, 2011, **41**, 687 and references therein.
5 (*a*) J. Jurczak and A. Golebiowski, *Chem. Rev.*, 1989, **89**, 149; (*b*) M. T. Reetz and D. Röhrig, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 1706; (*c*) L. K. Blasdel and A. G. Myers, *Org. Lett.*, 2005, **7**, 4281.
6 D. M. David, G. W. O'Meara and S. G. Pyne, *Tetrahedron Lett.*, 1996, **37**, 5417.
7 R. Kudirka, S. K. J. Devine, C. S. Adams and D. L. Van Vranken, *Angew. Chem., Int. Ed.*, 2009, **48**, 3677.
8 (*a*) K. Fagnou and M. Lautens, *Org. Lett.*, 2000, **2**, 2319; (*b*) M. Miyashita, T. Mizutani, G. Tadano, Y. Iwata, M. Miyazawa and K. Tanino, *Angew. Chem., Int. Ed.*, 2005, **44**, 5094.
9 Y. Yue, Y. Wang and W. Hu, *Tetrahedron Lett.*, 2007, **48**, 3975.
10 For recent reviews of hydrovinylations and codimerizations, see: (*a*) T. V. RajanBabu, *Synlett*, 2009, 853; (*b*) Y. Ura, H. Tsujita, T.-a. Mitsudo and T. Kondo, *Bull. Korean Chem. Soc.*, 2007, **28**, 2139. For selected recent papers, see: (*c*) B. Moreau, J. Y. Wu and T. Ritter, *Org. Lett.*, 2009, **11**, 337; (*d*) M. M. P. Grutters, J. I. van der Vlugt, Y. Pei, A. M. Mills, M. Lutz, A. L. Spek, C. Müler, C. Moberg and D. Vogt, *Adv. Synth. Catal.*, 2009, **351**, 2199; (*e*) N. Lassauque, G. Francio and W. Leitner, *Adv. Synth. Catal.*, 2009, **351**, 3133; (*f*) R. K. Sharma and T. V. RajanBabu, *J. Am. Chem. Soc.*, 2010, **132**, 3295; (*g*) J. Gavenonis, R. V. Arroyo and M. L. Snapper, *Chem. Commun.*, 2010, **46**, 5692; (*h*) W. Liu and T. V. RajanBabu, *J. Org. Chem.*, 2010, **75**, 7636; (*i*) I. Ayora, R. M. Ceder, M. Espinel, G. Muller, M. Rocamora and M. Serrano, *Organometallics*, 2011, **30**, 115.
11 (*a*) W.-J. Shi, Q. Zhang, J.-H. Xie, S.-F. Zhu, G.-H. Hou and Q.-L. Zhou, *J. Am. Chem. Soc.*, 2006, **128**, 2780; (*b*) Q. Zhang, S.-F. Zhu, X.-C. Qiao, L.-X. Wang and Q.-L. Zhou, *Adv. Synth. Catal.*, 2008, **350**, 1507; (*c*) Q. Zhang, S.-F. Zhu, Y. Cai, L.-X. Wang and Q.-L. Zhou, *Sci. China Chem.*, 2010, **53**, 1899; (*d*) Q.-S. Wang, J.-H. Xie, W. Li, S.-F. Zhu, L.-X. Wang and Q.-L. Zhou, *Org. Lett.*, 2011, **13**, 3388.
12 For other codimerizations of α,β-unsaturated ketone/esters with alkenes, see: (*a*) B. M. Trost, K. Imi and I. W. Davies, *J. Am. Chem. Soc.*, 1995, **117**, 5371; (*b*) F. Kakiuchi, Y. Tanaka, T. Sato, N. Chatani and S. Murai,, *Chem. Lett.*, 1995, 679; (*c*) T. Sato, F. Kakiuchi, N. Chatani and S. Murai, *Chem. Lett.*, 1998, 893; (*d*) M.-O. Simon, R. Martinez, J.-P. Genêt and S. Darsesa, *Adv. Synth. Catal.*, 2009, **351**, 153; (*e*) H. Tsujita, Y. Ura, K. Wada, T. Kondo and T.-a. Mitsudo, *Chem. Commun.*, 2005, 5100; (*f*) H. Tsujita, Y. Ura, S. Matsuki, K. Wada, T.-a. Mitsudo and T. Kondo, *Angew. Chem., Int. Ed.*, 2007, **46**, 5160; (*g*) C.-Y. Ho, H. Ohmiya and T. F. Jamison, *Angew. Chem., Int. Ed.*, 2008, **47**, 1893; (*h*) S. Ogoshi, T. Haba and M. Ohashi, *J. Am. Chem. Soc.*, 2009, **131**, 10350; (*i*) K.-H. Kwon, D. W. Lee and C. S. Yi, *Angew. Chem., Int. Ed.*, 2011, **50**, 1692; (*j*) Y. Hiroi, N. Komine, M. Hirano and S. Komiya, *Organometallics*, 2011, **30**, 1307.
13 (*a*) A. I. Meyers, M. A. Gonzalez, V. Struzka, A. Akahane, J. Guiles and J. S. Warmus, *Tetrahedron Lett.*, 1991, **32**, 5501; (*b*) S. M. Allin, S. L. James, W. P. Martin, T. A. D. Smith and M. R. J. Elsegood, *J. Chem. Soc., Perkin Trans. 1*, 2001, 3029; (*c*) C. Camarero, I. González-Temprano, E. Lete and N. Sotomayor, *Synlett*, 2007, 1101.