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Graphical Abstract

Ruthenium catalyzed regioselective coupling of terminal alkynes, amine and carbon dioxide leading to anti-Markovnikov adducts

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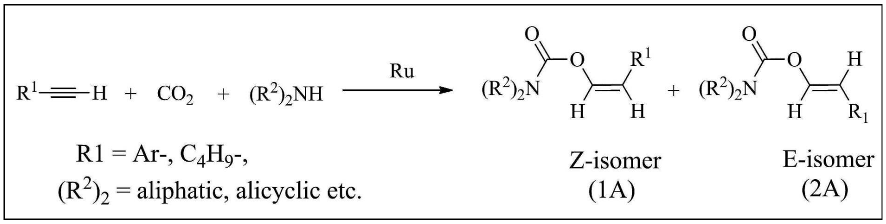

An efficient $RuCl_2$(*p*-cymene)/DPPE catalyzed addition of secondary amines and CO_2 to terminal alkynes were reported affording anti-Markovnikov adducts of alkenyl carbamates in good yield with excellent regioselectivity.

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Ruthenium catalyzed regioselective coupling of terminal alkynes, amine and carbon dioxide leading to anti-Markovnikov adducts

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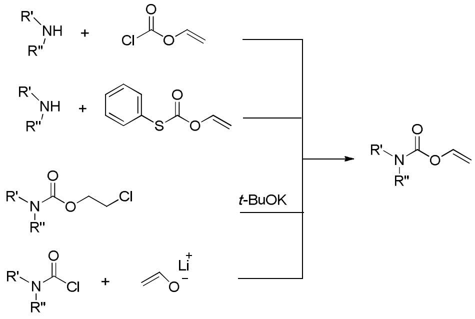
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

$RuCl_2$(*p*-cymene)/DPPE catalyzed addition of secondary amines and CO_2 to terminal alkynes afforded anti-Markovnikov adducts of vinyl carbamates in good yield with excellent regioselectivity is reported. The catalyst, consisting of labile *p*-cymene display very high regioselectivity towards the anti-Markovnikov adducts and was applicable to variety of aliphatic/aromatic alkynes and secondary amines.

In recent years, the use of carbon dioxide (CO_2) for the production of industrially important intermediates has attracted much more attention under the current background of the increase of emissions of CO_2.[1, 2] However, the activation of CO_2, a very stable molecule, is one of the biggest challenges in chemistry. Transition metal catalyzed transformation of CO_2 into vinyl carbamates, or enol carbamates is one of the attractive routes in CO_2 chemistry. Vinyl carbamates or enol carbamates are important building blocks, possessing wide application in agrochemicals, pharmaceuticals and are also essential monomers for transparent polymers and varnishes.[3a-b]

There are several synthetic pathways described for the preparation of vinyl carbamates in the literature (Scheme 1). Conventionally, alkyl carbamates synthesized via reaction of an amines with chloroformates,[4a-b] the dehydrohalogenation of α–halogeno,[5a-b] β–halogenoalkyl carbamates[6] and addition of amines to vinyl chloroformates (VOC-Cl).[7a-b] A reaction of VOC-Cl with an amine is mostly used for the preparation of vinyl carbamates (Scheme 1).[7b] These traditional synthetic methods are associated with several limitations including use of poisonous carbonyl source, use of toxic and difficult to handle intermediates, multiple reaction steps, low atom efficiency with a stoichiometric use of reagents which result in the formation of chemical waste. There are several efforts have been made to replace these toxic reagents by catalytic incorporation of CO_2 into organic substrate for their functionalization.[8a-c]

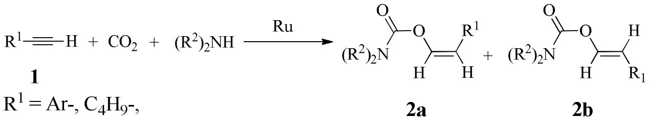


Scheme 1 Traditional synthesis of vinyl carbamates

Few groups have reported ruthenium based catalytic protocols for the synthesis of vinyl carbamates using carbon dioxide as C1 source like $RuCl_2$(norbornadiene)(pyridine)$_2$, [$RuCl_2$(norbornadiene)]$_n$, $Ru_3(CO)_{12}$, $RuCl_3$:$3H_2O$,[9a-b] bis-(n5-cyclooctadienyl)ruthenium, Ru-(COD)(COT)-tertiary phosphine and [$RuCl_2(C_5H_5N)_4$], [$RuCl_2(6\text{-}C_6H_6)(PMe_3)$].[10a-b] Despite of their potential utility, the above methods suffer from one or more drawbacks like lower yield and poor regioselectivity, requirement of expensive, air sensitive and toxic ligands which limits their application. Also, generality of the protocol has not been explored with respect to the structural and electronic variation of alkynes as well as amines. Therefore, there is a need to develop an active, stable, regioselective catalyst for the one pot synthesis of vinyl carbamates from carbon dioxide, amines and alkynes which could be worked efficiently under mild reaction condition, is a subject of the present work.

Low-valent ruthenium complexes have proven to be excellent catalysts for this transformation. The features of [$RuCl_2$(*p*-cymene)]$_2$, complex to spontaneously form a Ru-vinylidene in the presence of a terminal alkyne were tempted us to develop a system able to catalyze vinyl carbamates synthesis using carbon dioxide, secondary amines and alkynes.[11a-c]

Continuing our efforts towards the development of a new facile protocol for incorporation of CO_2 into organic chemicals,[12] here, we employed the $RuCl_2$(*p*-cymene)/DPPE as an efficient and highly active catalyst for regioselective synthesis of vinyl



1
R^1 = Ar-, C_4H_9-,
$(R^2)_2$ = aliphatic, alicyclic etc.

2a
Z-isomer

2b
E-isomer

Scheme 2 Ru-catalyzed synthesis of vinyl carbamate from CO_2

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†*Electronic Supplementary Information (ESI) available: Experimental, Characterization data of catalyst. See DOI: 10.1039/b000000x/*

carbamates using carbon dioxide, secondary amines and alkynes (Scheme 2).

In order to optimize the reaction conditions, initially the reactions of secondary amine and CO_2 to terminal alkynes were chosen as the model reaction. Various reaction parameters such as catalyst screening, catalyst loading, effects of solvents, and effect of CO_2 pressure, reaction temperature and time were investigated and the results obtained are summarized in Table 1 and 2.

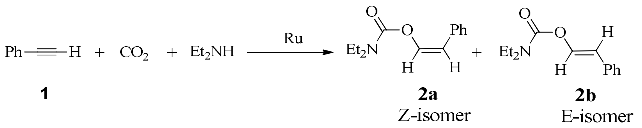
Firstly, we screened various metal complexes such as $RuCl_2/(TPPTS)_3$, $RuCl_2/(TPPTS)_3$/SILPC and β-diketonate complexe like $Ru(acac)_3$, $[Ru(TMHD)_3]$[12a] and $RuCl_3$-EDTA (Table 1, entries 1-5). It was observed that the complexes like $RuCl_2/(TPPTS)_3$, $RuCl_2/(TPPTS)_3$/SILPC gave lower conversion of desired product (up to 30%). Whereas, β-diketonate complexe gave 17% yield. The complexe involving *N*-containing ligand, $RuCl_3$-EDTA was found to be ineffective (Table 1, entry 5). Next we screened $RuCl_2$(*p*-cymene) as a catalyst which furnished 62% conversion of desired Z-isomer of the product. This increase in yield by using $RuCl_2$(*p*-cymene) precursor encouraged us to engage different phosphine ligands. Various phosphine containing ligands were screened for addition reactions of secondary amine and CO_2 to terminal alkynes. The best result was obtained by using DPPE as a ligand [DPPE = 1,1-bis(diphenylphosphino)ethane] (78%), while other ligands were found to give moderate yield of desired product (Table 1, entries 7 and 9). The $RuCl_2$(*p*-cymene)/DPPE (1:1 ratio) was found to be the best catalyst providing good yield (78%) of vinyl carbamate with an excellent Z/E ratio of 93:07 (Table 1, entry 8). The reactivity trend could results from the fact that there exist a labile *p*-cymene which could have displayed a very high regioselectivity towards the anti-Markovnikov adducts of alkenyl carbamates.

In transition metal-catalyzed reactions, the amount of catalyst employed proves to be an important aspect, considering this, the efforts were made to determine the optimum loading of the catalyst. We studied the catalyst loading ranging from 0.3 to 1.5 mol %, where increase in initial catalyst concentration up to 1.0 mol % has increased the yield of desired product (Table 1, entries 10–12) while further increase in the amount of catalyst had no profound effect on the yield of the desired product as well as selectivity (Table 1, entry 12).

The effect of different solvents on the reaction system was investigated and it was observed that nature of solvent affected the conversion of the reaction (Table 2, entries 1-7). The solvents like toluene, *N,N*-dimethylformamide (DMF), tetrahydrofuran (THF), 1,4-dioxane and acetonitrile (ACN) were screened for the standard reaction. However, among all the solvents screened ACN was found to furnish good yield and regioselectivity (Table 2, entry 4).

To examine the effect of reaction temperature on the yield of vinyl carbamates synthesis, the catalytic reaction of phenylacetylene, diethylamine and CO_2 were studied at different reaction temperature ranging from 60-100 °C (Table 2, entries 8–9). It was observed that at 60 °C the yield of the desired product was low whereas with increase in reaction temperature up to 80 °C, the yield and selectivity of vinyl carbamate towards the Z-isomer (2a) was found to increase in 24 h. Further increase in the temperature to 100 °C resulted in decreased yield and selectivity was observed (Table 2, entry 9).

Table 1 Effect of catalyst on vinyl carbamate synthesis from phenyl acetylene, diethyl amine and CO_2[a]



Entry	Catalyst (loading mol %)	Yield[b] (%)	Selectivity (**2a:2b**)
Catalyst screening			
1	$RuCl_3/(TPPTS)_3$ (1%)	20	65:35
2	$RuCl_2/(TPPTS)_3$/ SILPC (1%)	30	68:32
3	$Ru(acac)_3$(1%)	17	70:30
4	$[Ru(TMHD)_3]$ (1%)	50	77:23
5	$RuCl_3$-EDTA (1%)	trace	-
6	$[RuCl_2$(*p*-cymene)$]_2$ (1%)	62	78:22
7	$[RuCl_2$(*p*-cymene)$]_2/PPh_3$ (1%)	70	91:09
8	$[RuCl_2$(*p*-cymene)$]_2$/DPPE (1%)	78	93:07
9	$[RuCl_2$(*p*-cymene)$]_2$/DPPB (1%)	75	91:09
Catalyst Loading			
10	$[RuCl_2$(*p*-cymene)$]_2$/DPPE (0.3%)	43	92:08
11	$[RuCl_2$(*p*-cymene)$]_2$/DPPE (0.6%)	64	92:08
12	$[RuCl_2$(*p*-cymene)$]_2$/DPPE (1.5%)	78	93:07

[a] Reaction conditions: phenyl acetylene (2 mmol), diethyl amine (4 mmol), metal:Ligand ratio (1:1), ACN(10 ml), CO_2 pressure (5 MPa), Temp. (80°C), Time (24 h). [b] Yield based on GC analysis

Table 2 Effect of reaction parameters on vinyl carbamate synthesis from phenyl acetylene, diethyl amine and CO_2[a]

Sr. No	Solvent	Temp (°C)	CO_2 (MPa)	Time (h)	Yield[b] (%)	Selectivity (**2a** : **2b**)
Effect of solvent						
1	Toluene	80	5	24	30	90:10
2	DMF	80	5	24	15	89:11
3	THF	80	5	24	49	93:07
4	ACN	80	5	24	78	93:07
5	1, 4-Dioxane	80	5	24	21	90:10
6	Glycerol	80	5	24	50	88:12
7	Water	80	5	24	10	-
Effect of temperature						
8	ACN	60	5	24	38	93:07
9	ACN	100	5	24	54	89:11
Effect of CO_2 pressure						
10	ACN	80	3	24	47	77:23
11	ACN	80	4	24	70	93:07
12	ACN	80	7	24	80	91:09
Effect of time						
13	ACN	80	5	12	62	93:07
14	ACN	80	5	18	69	93:07
15	ACN	80	5	30	80	93:07

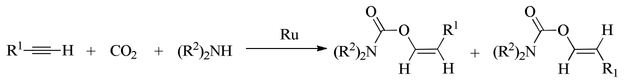
[a] Reaction conditions: phenyl acetylene (2 mmol), diethyl amine (4mmol), catalyst (1 mol%), DPPE (1mol %), ACN(10 ml), CO_2 pressure (5 MPa), Temp. (80°C), Time (24 h). [b] Yield based on GC analysis

The influence of CO_2 pressure for vinyl carbamates synthesis was then investigated. It was observed that increasing the pressure from 4 MPa to 5 MPa resulted increase in the yield and selectivity of the Z-isomer (Table 2, entries 10–12). Further increase in the pressure to 7 MPa had no profound effect on the reaction yield and selectivity (Table 2, entry 12). Hence, the best optimized reaction parameters for regioselective synthesis of vinyl carbamates were phenylacetylene, diethylamine and carbon dioxide are: $Ru[Cl_2(p\text{-cymene})]_2$ (1.0 mol %), DPPE (1 mol%), solvent (ACN, 10 mL), diethylamine (4 mmol), CO_2 pressure (5 MPa), temperature 80 °C, time 24 h.

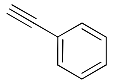
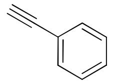
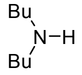
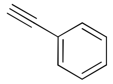
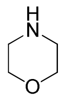
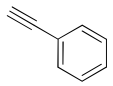
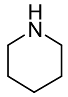
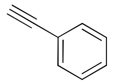
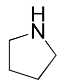
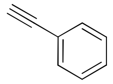
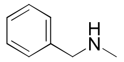
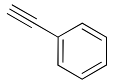
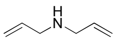
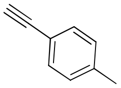
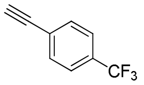
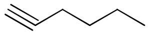
With these optimized reaction conditions in hand, we investigated the scope and generality of the developed protocol for the synthesis of variety of vinyl carbamates. Various alkynes and secondary amines with different steric and electronic properties were screened (Table 3, entries 1-10). The addition reaction of diethyl amine and CO_2 to phenylacetylene under the optimized reaction conditions providing a 78 % isolated yield of the [(diethylcarbamoyl)oxy]styrene and (Z)-β-[(diethylcarbamoyl)oxy]styrene isomer with 93:07 selectivity and along with small amount of dimmer of phenyl acetylene as biproduct. Dibutyl amine was also found to react efficiently with phenyl acetylene providing an excellent selectivity of (Z)-β-[(dibutylcarbamoyl)oxy]styrene isomer up to 91%. Alicyclic amines like morpholine and piperidine were found to provide good yield and selectivity of [(morpholinocarbamoyl)oxy]styrene and [(piperidinocarbamoyl)oxy] styrene isomer respectively (Table 3, entries 3–5). Further we screened *N*-methyl-1-phenylmethanamine and diallylamine and were found to furnish good yield and selectivity toward the formation of desire product (Table 3, entries 6–7).

The present catalytic system was also worked well with the electron donating and withdrawing aromatic substituted alkynes providing good conversions with excellent selectivity (Table 3, entries 8-9). Moreover, we also studied the aliphatic alkyne such as 1-hexyne; reacted under the present conditions to afford moderate yield of [(diethylcarbamoyl) oxy]hex-1-ene (Table 3, entry 10). Thus, improved yield and excellent selectivity was observed for various vinyl carbamates under the developed catalytic protocol as compared to earlier reports.

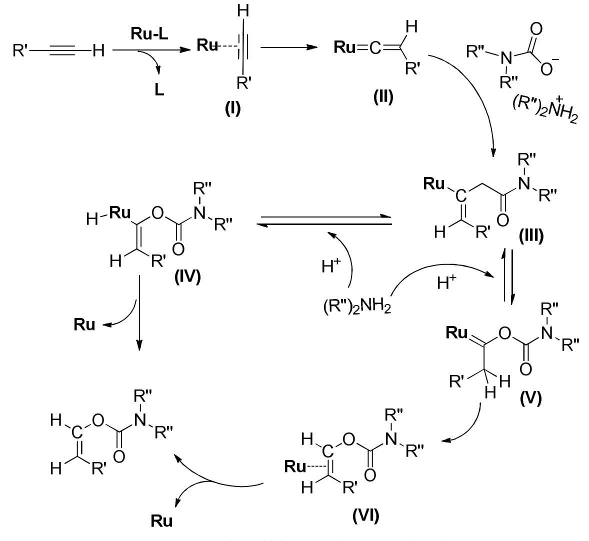
Table 3 The synthesis of vinyl carbamates from alkynes, secondary amines and CO_2[a]



1 **2a** Z-isomer **2b** E-isomer

Entry	Alkynes (R^1)	Secondary amines (R^2)	Yield[b] (%)	Selectivity **2a**:**2b**
1		Et_2NH	78	93:07
2			61	91:09
3			47	89:11
4			63	90:10
5			49	88:12
6			87	97:03
7			84	98:02
8		Et_2NH	63	93:07
9		Et_2NH	57	89:11
10		Et_2NH	48	77:23

[a]Reaction conditions: Alkynes (2 mmol), secondary amine (4 mmol), catalyst (1 mol %), DPPE (1 mol %), ACN (10 ml), CO_2 pressure (5 MPa), temp (80 °C), time (24 h).



Scheme 3 Plausible reaction mechanism

The plausible mechanism of addition reactions of secondary amine and CO_2 to terminal alkynes for vinyl carbamate synthesis was shown in Scheme 3. Firstly, the rearrangement of ruthenium complex of type (I) into metal derivatives of type (II) takes place, which show electrophilic behavior of the carbon atom bonded to the metal center. Subsequent addition of carbamates to the electrophilic carbon of this vinylidene-ruthenium molecule (II) to give the intermediate (III).[13] Subsequently, the ammonium cation $[(R^2)_2NH_2^+]$ formed during the course of reaction which protonates the Ru metal followed by classical reductive elimination from (IV), leading to the enol carbamate. An alternative route could be protonolysis of the Ru-C bond (III) followed by 1-2 shift of hydrogen atom giving intermediate (VI), which on further de-coordination afford desired product.[14]

In summary, $RuCl_2(p\text{-cymene})$/DPPE catalytic system has shown to be an efficient transition-metal catalyzed process for the synthesis of alkenyl carbamates *via* three-component addition of secondary amines and CO_2 to terminal alkynes. The characteristic feature of present catalytic protocol is the high regioselectivity giving the anti-Markovnikov adducts in good to excellent yield. The different alkynes and secondary amines with different steric and electronic properties were explored for synthesis of alkenyl carbamates. The catalyst is highly stable and shows an excellent catalytic activity under optimized condition make it an ideal catalyst for regioselective synthesis of vinyl carbamate.

Acknowledgment

The author (R. A. Watile) is greatly thankful to Council of Scientific and Industrial Research (CSIR, India) for providing financial support (CSIR-SRF).

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Experimental

All chemicals and reagents were purchased from firms of repute with their highest purity available and were used without further purification. $[RuCl_2(p\text{-cymene})]_2$ precursor and phosphine ligands were purchased from Sigma-Aldrich. The reaction mixture was analyzed by GC (Perkin-Elmer, Clarus 400) equipped with a flame ionization detector (FID) and a capillary column (Elite-1, 30 m × 0.32 mm × 0.25 μm). The crude product was purified by column chromatography on silica gel (eluting with 80:20 petroleum ether/ethyl acetate) to afford the product.

General procedure for synthesis of vinyl carbamate from CO_2

In a typical experimental procedure, the alkynes (2 mmol), secondary amine (4 mmol), $[RuCl_2(p\text{-cymene})]_2$ (1 mol %), DPPE (1 mol %) and ACN (10 ml) were charged into a 100 ml stainless steel autoclave with a mechanical stirrer at room temperature. The autoclave was flushed with carbon dioxide and reaction mixture was then pressurized to 5 MPa of CO_2 pressure; the reactor was heated to 80 ^oC and stirred for 24 h at 600 rpm. After completion of reaction, the reactor was cooled to room temperature and the remaining carbon dioxide was carefully vented and then the reactor was opened. The crude product which was then purified by column chromatography on silica gel (100–200 mesh size), with petroleum ether/ethyl acetate (PE–EtOAc, 80:20) as eluent to afford a pure product. The products were further characterized by GCMS analysis, ^1H NMR and ^{13}C NMR spectra (Varian 300 MHz NMR Spectrometer) using TMS as internal standard. GCMS analysis was done on Shimadzu-QP2010 mass spectrometer (Shimadzu GC-MS QP 2010) (Rtx-17, 30 m x 25 mm ID, film thickness 0.25 mm df) (column flow 2 mL min-1, 80 ^oC to 240 ^oC at 10 ^oC min-1. rise).