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Intermolecular Cross-Double-Michael Addition between Nitro and Carbonyl Activated Olefins as a New Approach in C–C Bond Formation

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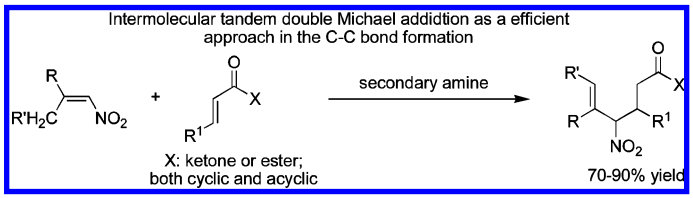
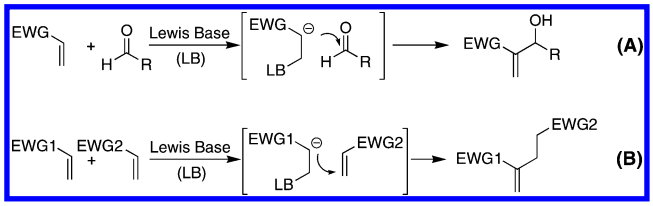
ABSTRACT



A novel intermolecular cross-double-Michael addition between nitro and carbonyl activated olefins has been developed through Lewis base catalysis. The reaction took place with a large group of *β*-alkyl nitroalkenes and *α*,*β*-unsaturated ketone/esters, producing an allylic nitro compound in good to excellent yields.

Efficient C−C bond formation and implementation of diverse functionality are two crucial aspects in organic synthesis.[1] In the last two decades, tandem (or cascade or sequential) reactions of designated precursors brought great attention to the construction of complicated organic molecules.[2] Significant progress has been made using this strategy in the total synthesis of natural products and biological activated molecules.[3] Meanwhile, intermolecular sequential reactions across different reactants have been developed into many powerful methodologies, including the Mannich reaction,[4] the Baylis−Hillman reaction,[5] and the Robinson annulations,[6] etc. The fact that tandem reactions of different substrates can rapidly combine organic functionalities within "one step" provides undeniable benefits as a simple, efficient, and atom-economical approach in organic synthesis.

Our interests in developing new organic reactions with the capability of rapid functional group construction originated from the Lewis base (LB) mediated Baylis−Hillman reaction (reaction A). As shown in reaction B, the successful intermolecular cross-double-Michael addition will lead to very attractive products in one step and provide a highly efficient novel methodology in complex molecule synthesis.



According to the literature, the only successful example using this strategy is the homodimerization of enones by

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(1) (a) Corey, E. J. *Angew. Chem., Int. Ed.* **1991**, *30*, 455−465. (b) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544−4568. (c) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067−2096. (d) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442−4489.

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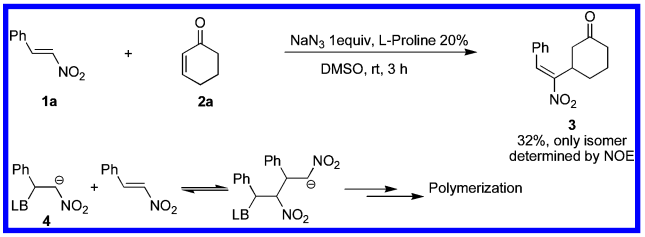
action of an organophosphine, which is referred to as the Rauhut−Currier reaction.[7] Although this reaction was first discovered in 1963, no related reactions have been reported until very recently, when the Krische group,[8] the Miller group,[9] and the Wang group[10] developed effective intramolecular asymmetric cyclization of α,β-unsaturated ketones. In addition, the Kwon group successfully applied organophosphine catalysts to promote both intermolecular and intramolecular allene−alkene coupling.[11] These remarkable works re-emphasize the advantages of this reaction as a very attractive approach in C−C bond construction. However, to date, there is still a lack of effective methodology for efficient intermolecular cross-coupling of different activated olefins, especially non-ketone/aldehyde Michael receptors, which essentially will provide more functionality in the final products.[12] In this paper, we report the first successful intermolecular double-Michael addition between nitro and carbonyl activated olefins through LB-catalyzed cascade reactions.

The biggest challenge for the cross-double-Michael addition is the control of sequential addition across the two Michael receptors. Assuming that the EWG1 activated alkene is more reactive than the EWG2 activated alkene, the nucleophilic addition of the LB catalyst will first attack the EWG1 olefin, forming the carbanion intermediate. However, the carbanion intermediate will most likely react with the EWG1 activated olefin (homoaddition) rather than the EWG2 activated olefins (desired heteroaddition). This fundamental challenge was associated with all of these types of reactions and directly resulted in no observation of successful hetero-double-Michael addition in the literature, although this methodology is extremely interesting for synthetic organic chemists.

To investigate this reaction, we first studied the reaction between the nitro and carbonyl activated olefins. It is well-known that the nitroalkenes are more reactive Michael receptors than enones, which makes the sequential addition across the two alkenes possible. The β-nitrostyrene was then used to react with various carbonyl-activated alkenes, including cyclohexenone, methyl acrylate, and methyl vinyl ketone. Meanwhile, various Lewis bases were applied to promote this reaction, including DMAP, PPh_3, DABCO, imidazole, and NMI. However, among all the tested conditions, polymerization of nitroalkene dominated, and only a trace amount of the desired product was obtained, except when both proline and NaN_3 were used as the catalysts, which produced 32% of the desired product as a single *E* isomer (determined by NOE) (Scheme 1). No product was isolated if only proline or only NaN_3 was used as the catalyst.

Scheme 1



Monitoring this reaction in d_6-DMSO by NMR revealed that almost all the β-nitrostyrene was consumed in 1 h, and formation of product **3** was not observed until 2 h later, when most of **1a** had already been consumed (Supporting Information). These results strongly implied that the addition of nitrocarbanion **4** to β-nitrostyrene (which leads to the polymerization) is in equilibrium, and intermediate nitroalkene oligomers can dissociate and reproduce the nitrocarbanion **4**, leading to the addition of a less reactive enone Michael receptor. Therefore, the key for successful intermolecular hetero-double-Michael addition is to avoid the polymerization and "quench" the equilibrium by a kinetically irreversible step. Thus, the α-methyl-β-nitrostyrene **1b** was employed to react with enone **2a**. The purpose for using **1b** is to: (a) slow the nitroalkene polymerization and (b) introduce an irreversible step by the alkyl group β-elimination. As expected, the allylic nitro product **5a** was formed in good yields. The results of reaction condition screening are shown in Table 1.

Among all of the tested Lewis bases, the secondary amines were the only effective catalysts that promoted this reaction (entries 1, 4, and 5). The non-nucleophilic amine (DIPEA, entry 7) and primary amine (glycine, entry 6) did not promote this reaction, while the nucleophilic tertiary amine (DABCO, entry 3) promoted the reaction with slow kinetics and poor yield. The inorganic base (NaOt-Bu, entry 8) gave significant polymerization of **1b** with no desired product obtained. Meanwhile, other nucleophilic bases (entry 9), including DMAP, imidazole, NMI, PPh_3, and $P(OMe)_3$, all proved as noneffective catalysts for this reaction. Combination of proline (0.2 equiv) and other Lewis bases revealed modified reaction conditions (entries 10−14), and NaN_3 was selected as the best adduct. Finally, the solvent screening gave DMSO as the most effective solvent. With the best reaction conditions, various nitroalkenes and α,β-unsaturated ketones and esters were applied to investigate the reaction substrate scope, and the results are summarized in Table 2.

As shown in Table 2, various nitroalkenes and α,β-unsaturated ketones/esters are all suitable for this transformation. Good to excellent yields were obtained in most cases,

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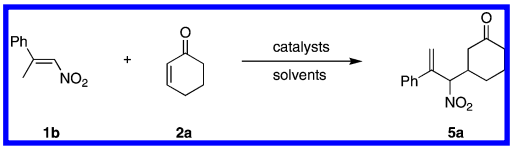
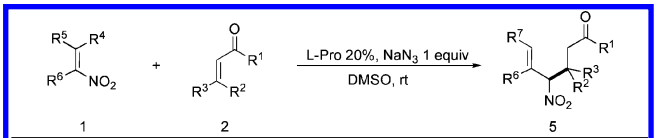
Table 1. Screening of the Reaction Conditions[a]

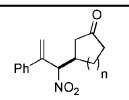
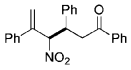
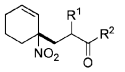
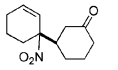
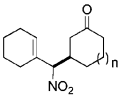
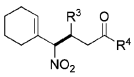
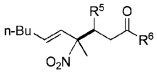
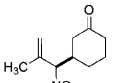
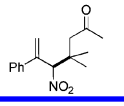


	solvent	Lewis base (equiv)	co-cat (1.0 equiv)	time (h)[b]	convn (%)[c]	yield (%)[d]
1	DMSO	L-Pro (0.2)	–	4	93	80
2	DMSO	NaN_3 (1.0)	–	9	55	6
3	DMSO	DABCO (1.0)	–	12	50	20
4	DMSO	pyrrolidine (0.2)	–	4	72	60
5	DMSO	pyrrolidine (0.2)	AcOH	4	100	81
6	DMSO	glycine (1.0)	–	20	trace	trace
7	DMSO	DIPEA (1.0)	–	20	trace	trace
8	DMSO	NaOt-Bu (1.0)	–	4	100	trace
9	DMSO	other bases[e]	-	20	trace	trace
10	DMSO	L-Pro (0.2)	DIPEA	4	100	76
11	DMSO	L-Pro (0.2)	DMAP	4	100	86
12	DMSO	L-Pro (0.2)	PPh_3	4	100	83
13	DMSO	L-Pro (0.2)	NaN_3	3	100	90
14	DMSO	L-Pro (0.2)	DABCO	4	100	21
15	THF	L-Pro (0.2)	NaN_3	20	trace	trace
16	H_2O	L-Pro (0.2)	NaN_3	20	trace	trace
17	MeOH	L-Pro (0.2)	NaN_3	5	95	72
18	$MeNO_2$	L-Pro (0.2)	NaN_3	20	40	31
19	acetone	L-Pro (0.2)	NaN_3	5	9	8

[a] Reactions were carried out at room temperature, **1b**/**2a** = 1:2. [b] Reaction time was determined by TLC. [c] Conversion based on the consumption of the starting material **1b** from NMR. [d] **5a** as a mixture of syn/anti diastereomers (dr = 1:1), and the NMR yield was determined by 1,3,5-trimethoxybenzene as the internal standard. [e] Other bases tested include 1.0 equiv of DMAP, imidazole, NMI, PPh_3, and $P(OMe)_3$.

Table 2. Reaction Substrate Scope[a–c]



compounds		time (h)	dr	yield (%)[b]
	**5a**: n=2	3	1.0:1	87
	5b: n=3	5	1.2:1	72
	5c: n=1	8	1.1:1	55
	**5d**	5	1.6:1	70
	**5e**: R^1=H, R^2=Me	6	-	90
	5f: R^1=H, R^2=OMe	6	-	85
	5g: R^1=R^2=Me	6	2:1	92
	**5h**	3	1.3:1	76
	**5i**: n=1	3	1.2:1	90
	5l: n=2	5	1.0:1	76
	**5j**: R^3=R^4=Ph	12	4:1	70
	5k: R^3=R^4=Me	5	1.6:1	81
	**5m**: R^5=R^6=Me	4	1.1:1	82
	5n: R^5=H, R^6=OMe	3	-	70
	**5o**	6	1.1:1	70
	**5p**	6	-	45

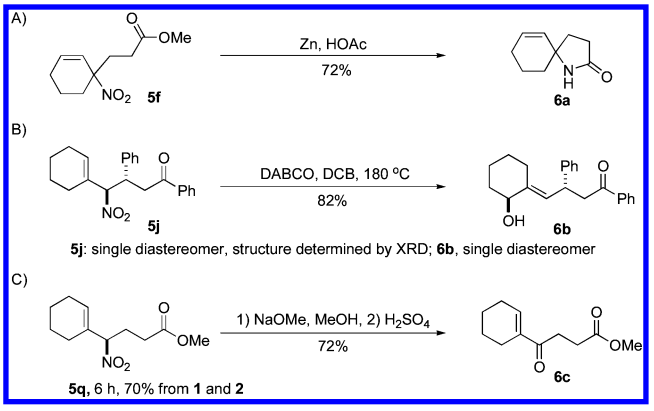
[a] Same conditions as in Table 1. [b] Isolated yield. [c] The relative stereochemistry of **5d** was determined by X-ray crystallography.

including kinetically hindered cyclopentene **5c** and β-disubstituted enone **5p**. Similar reactivities between enone and ester were observed (**5e** and **5f**), which clearly indicated that the formation of iminium between enone and proline was unnecessary for the reaction. This result is consistent with the fact that low enantioselectivity (<5% ee) was observed in all tested cases. Similar to other nitro chemistry, low diastereoselectivity was obtained due to the acidic proton on the nitro carbon (e.g., **5a** and **5l**) or the similar stereo effect by alkyl and nitro groups (e.g., **5g** and **5m**). However, the low dr could be a small problem since the two diastereomers can be either separated or converted into the same product through readily available nitro chemistry. Three examples are shown in Scheme 2 to convert the allylic nitro compounds into amine (lactam), allylic alcohol, and enone with good yields.

Considering the fact that proline itself can promote this reaction without NaN_3 (Table 1, entry 1), the secondary amine most likely serves as the LB catalyst while NaN_3 helps by tuning the reaction acidity for optimal performance. One key mechanistic question is whether this reaction underwent nucleophilic addition to nitroalkene followed by the second Michael addition or just through γ-carbon deprotonation.

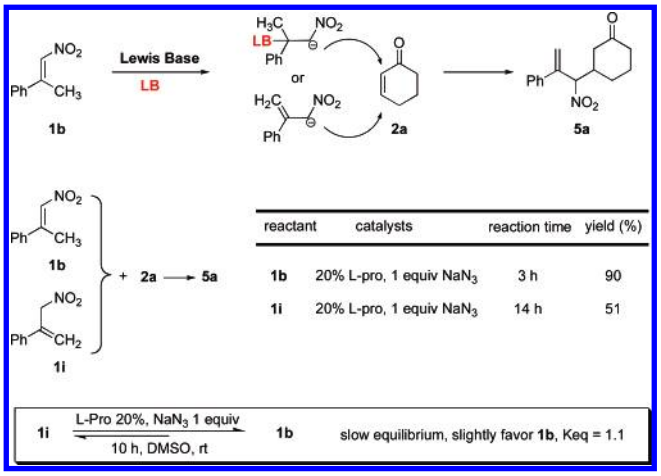
As indicated in Table 1, the secondary amines were the only effective catalysts. Both the non-nucleophilic amine (Hünig's base, entry 7) and the primary amine (entry 6) did not catalyze this reaction and revealed the importance of the catalyst nucleophilicity for effective promotion of the reaction. Meanwhile, the addition of acid to pyrrolidine accelerated the reaction (entry 5), providing additional evidence that

Scheme 2



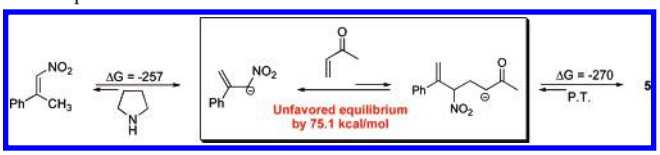
disfavors the carbanion path. To further investigate the mechanism, compound **1i** was synthesized and applied into the reaction with **2a** as a comparison with the reaction between **1b** and **2a**. As shown in Scheme 3, a clear kinetic

Scheme 3. Possible Reaction Mechanism



difference was observed between **1b** and **1i**. These experimental results strongly suggested the LB nucleophilic mechanism as proposed. This hypothesis was further supported by computational studies. An energetically unfavored equilibrium between allylic nitro carbanion and enone was observed (Scheme 4), which may explain why the simple deprotonation of the γ-carbon could not lead to the desired product.

Scheme 4. Computational Studies Revealed the Unfavored Equilibrium for the Carbanion Second Michael Addition



In conclusion, by introducing the β-alkyl group in the nitroalkene, we developed the first successful intermolecular double-Michael addition. Many different nitro- and carbonyl-activated olefins were suitable for this reaction. The products are synthetically attractive and can be readily converted into many other complex building blocks. Although the reaction mechanism remains to be further elucidated, this reaction provides a new approach for C−C bond formation under mild, efficient, and atom-economic reaction conditions. Asymmetric synthesis and conversion of the final product into other attractive building blocks are under investigation.

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Supporting Information Available: Experimental and computational details, spectrographic data, and XRD information. This material is available free of charge via the Internet at http://pubs.acs.org.

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